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ApoE Risk Disclosure: A Review of Positive and Negative Outcome

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Abstract

Two of this century's most significant healthcare challenges are Alzheimer's disease and mild cognitive impairment, with 40 million people suffering from the diseases. In fact, a conservative estimate projects that both conditions will double every 20 years until 2050. Alzheimer's disease involves memory impairment, disorientation, confusion, and various problematic behaviors. Presently, no prevention method or cure has been discovered for Alzheimer's. Mild cognitive impairment typically includes problems with memory, language, thinking, and judgment beyond those typical of one's age. Usually, these symptoms do not interfere with daily activities but do not improve and have been linked with a risk of developing Alzheimer's as time goes on. As research in this area has evolved, genetic biomarkers have been discovered that determine the potential risk of Alzheimer's disease. While there are no guarantees that individuals will develop Alzheimer's, they can increase the likelihood of disease onset. Despite the potential for life changes and behaviors that could reduce disease risk, most health professionals are unwilling to disclose these biomarkers to their patients. Clinicians' perceived risk and biases in believing that disclosing this biomarker will harm patients can result in patients receiving limited health information in this area. However, the debate surrounding this disclosure as harmful to patients should be informed by objective outcomes, rather than only perceived harm. This literature review examines the objective outcomes of genetic risk disclosure and ethical guidelines relevant to any disclosure(s).

APOE RISK DISCLOSURE: A REVIEW OF POSITIVE AND NEGATIVE OUTCOMES

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CHAPTER I: A REVIEW OF POSITIVE AND NEGATIVE OUTCOMES OF APOE RISK DISCLOSURE

Overview of Alzheimer's, Mild Cognitive Impairment, and ApoE Disclosures

Alzheimer's disease (AD) and mild cognitive impairment (MCI) are two of this century's most significant healthcare challenges, with 40 million people currently suffering from the diseases. Progressive AD and MCI is expected to double every 20 years until 2050 (Alzheimer's Association [AA], 2020a). The Alzheimer's Association defines AD as a degenerative brain disease caused by complex changes within the brain that result in cell damage (AA, 2020a).

Over time, this disease gradually worsens the symptoms, including problems remembering new information that affects the brain's learning area. AD symptoms increase in severity and can include disorientation, confusion, and behavior problems. Physically, an individual can also experience difficulties walking and swallowing. Unfortunately, AD has no prevention method or cure (AA, 2020a).

The Diagnostic and Statistical Manual of Mental Disorders (5th ed.*; DSM-5*; American Psychiatric Association, 2013) requires certain criteria be met before a diagnosis of AD can be made. An AD diagnosis requires that an individual meet criteria for a major or mild neurocognitive disorder, including objective neuropsychological testing evidence of a significant or modest cognitive decline in previous performance within at least one cognitive domain (APA, 2013). The cognitive domains involved include: complex attention, executive functioning, learning and memory, language, perceptual-motor, or social-cognition. In addition, the individual's daily functioning must also reveal cognitive deficits interfering with daily activities (e.g., paying bills, managing medications; APA, 2013). Further, these declines cannot occur

during a diagnosis of delirium or be better explained by another mental health illness such as anxiety or depression (APA, 2013).

A diagnosis of major or mild neurocognitive disorder due to AD further requires a gradual onset and progression with impairment in one or more of the cognitive domains previously mentioned (APA, 2013). A diagnosis of probable AD must also have either 1) evidence of genetic mutation (e.g., from family history or genetic testing), or 2) clear evidence of memory and learning decline in one cognitive domain; a decline in cognition that is steady, progressive and gradual; and the absence of other neurodegenerative or cerebrovascular disease (e.g., multiple sclerosis, Parkinson's, Huntington's, ALS; APA, 2013). Probable AD when compared to possible AD is differentiated based on whether or not there is evidence of AD. Possible AD involves clear evidence of memory and learning decline; steady, progressive, and gradual decline in cognition absent of any plateaus; and no evidence of mixed causes for the decline. Possible AD requires that the decline not be better explained by either a cerebrovascular or another neurodegenerative disease. The decline can also not be a result of the effects of substances or another mental health condition (APA, 2013).

The DSM-5 definition of MCI falls under the criteria mentioned above for a mild neurocognitive disorder. This definition has evolved over time. In 1980 the DSM-III referred to it as an early dementia stage, while the Clinical Dementia Rating (CDR) and Global Deterioration Scale (GDS) published dementia predecessors such as "questionable dementia" and "mild cognitive decline" (Reisberg et al., 2008, p. 18). In 2001, a definition of MCI was created (Reisberg et al., 2008, p. 18). Petersen set forth an MCI decision process for clinicians when looking at memory impairment which involved amnestic and non-amnestic MCI that was

then split into either single or multiple domain MCI (Petersen, 2004). He reinforced the importance of realizing that MCI is ultimately a clinical diagnosis where clinicians use their judgment with procedures and assessments available to assist them in the process (Petersen, 2004).

In fact, MCI evolved as early as the 1990's, defining the early clinical signs of AD in those individuals unable to meet the criteria for an AD diagnosis (Bradfield, 2021). Essentially, MCI is defined as a prodromal state of cognitive decline that is more than the normal aging process and may be the early manifestations of AD (Golomb et al., 2004). The modern definitions of MCI include the following features: subjective decline in cognition, objective psychometric impairment, and relative preservation of an individual's activities of daily living (ADLs; Bradfield, 2021). During this more recent analysis it was noted that each MCI definition can vary slightly in how the above-mentioned features are utilized. Bradfield (2021) pointed out that the subjective decline for MCI originally established by Petersen could be lacking sensitivity for those individuals without awareness or insight regarding their level of cognitive impairment. Therefore, collateral source informants and clinicians are also utilized now when determining subjective cognitive decline. Further, the objective psychometric impairments now look at several cognitive domains when determining a decline, not just memory as they did in the past (Bradfield, 2021).

The conversion from MCI to AD was found to typically occur over a 5-year time period with an annual conversion rate of 10-12% (Petersen et al., 1999). Notable is the fact that some individuals with MCI remain stable without any additional decline (Golomb et al., 2004).

According to the Mayo Clinic (2023), MCI exists between the expected cognitive decline during normal aging and the more serious decline of dementia. MCI involves problems with memory, language, thinking, and judgment beyond those typical of one's age. The individual or their family and friends may notice the symptoms, which do not usually interfere with daily activities. While MCI might or might not increase one's risk of later developing Alzheimer's disease, few with this condition get better (Mayo Clinic, 2023). This potential connection between MCI and AD results in the inclusion of both types of participants during some clinical research studies.

Currently, there is limited knowledge regarding the etiology and curative treatments for AD and MCI (Roberts et al., 2014). However, there have been scientific breakthroughs in AD and MCI research. Current research has identified two categories of genes influencing whether a person may develop AD: 1) risk genes and 2) deterministic genes (AA, 2020b).

Risk genes do not guarantee that one will develop AD, but they increase the likelihood of disease onset (AA, 2020b). For example, in 2010, the National Institutes of Health (NIH) discovered a risk gene during human genome testing, identified as the Apo lipoprotein E gene (ApoE) with three allele versions: ε2, ε3, and ε4. This ApoE gene combines with body lipids, creating lipoproteins that carry cholesterol and other fats through the bloodstream. The ApoE-ε4 risk gene was identified first and appears to have the strongest impact on AD risk, with 40%–65% of AD-diagnosed individuals having the gene (AA, 2020b)

Individuals inherit some form of ApoE from each parent. Those who inherit ApoE-ε4 from both parents have a much higher risk for AD, but even then, AD is not guaranteed. In 2017, Sabbagh et al. found that this biomarker helped to improve the clinical diagnosis of AD from

55% to 84% accuracy. Approximately 20%–30% of individuals within the US have one or two copies of ApoE-ε4. The ApoE-ε4 gene has been found to be a strong genetic risk factor for AD (Situmeang et al., 2016). In fact, during Situmeang's 2016 research study of 60 participants (23 with normal aging, 17 with amnestic MCI, and 20 with AD), the participants carrying the ApoE-ε4 allele were 3.9 times more likely to have AD than the non-carrier participants (Situmeang et al., 2016). In addition, Situmeang et al. discovered a correlation between the ApoE-ε4 gene, Aβ plasma level, and the progression of AD in research participants (2016). This study suggested that the onset of AD symptoms may, in fact, be earlier than usual in ApoE-ε4 individuals (AA, 2020b).

In contrast, deterministic genes are known to directly cause AD, guaranteeing that those who inherit these genes will develop the disease (AA, 2020b). To date, research scientists have found these rare genes for AD in only a few hundred families around the world, accounting for 1% or less of the early onset AD cases (e.g., developing in their 40s and 50s; AA, 2020b). The typical onset for AD occurs at 65 years old or older. The discovery of these genes has revealed important information regarding the etiology of AD as the gene's effect on the processing and production of beta-amyloid, the protein constituting the deadly plaques responsible for the decline and death of brain cells. AD has been associated with the clearance of amyloid beta (Aβ) plasma in the brain (Situmeang et al., 2016). Presently, numerous drugs are being used with AD patients to target beta-amyloid to slow or stop the progression of this disease (AA, 2020b). Two ongoing international investigations also study individuals with the AD deterministic gene (AA, 2020b).

Clinically, “age-associated cognitive decline” has often been used to describe “normal aging” and is defined by an individual’s performance on standardized cognitive tests examining learning, memory, attention, processing speed, language, and visuo-constructional skills (Janoutová et al., 2015). Reisberg first introduced the term “mild cognitive impairment” in 1982 (Reisberg et al., 2008). Then, in 2004, Petersen adopted the term to describe a period during neurodegenerative disease when one’s cognitive skills are no longer normal for their age, but daily functioning has not been interrupted to fit a dementia diagnosis (Petersen, 2004). As science progressed, MCI was further distinguished into two forms: amnestic and non-amnestic (Petersen & Morris, 2005). They also discovered that these two types of MCI might have differing etiologies, such as vascular dementia or AD (Petersen & Morris, 2005).

The focus on prodromal MCI as a condition of AD began in 1999, emphasizing the importance of memory impairment for the early stages of AD (Petersen et al., 2009). However, at that time it was also noted that not all forms of MCI would become AD, with researchers indicating that a broader conceptualization of MCI was needed. In 2003, a conference of international experts on MCI was held with the specific purpose of revising the criteria for MCI. This conference expanded the MCI criteria and created the National Institute on Aging Foundation (NIAF) funded by the Alzheimer Disease Centers Program Uniform Data Set and public-private neuroimaging/biomarker consortium, along with the Alzheimer Disease Neuroimaging Initiative (Petersen et al., 2009). The criteria created at this time generated the two clinical phenotypes of MCI – amnestic MCI (aMCI) and nonamnestic MCI (naMCI) which many research studies have used to analyze the utility and prognosis of disease diagnoses (Petersen et al., 2009).

The conversion rate for individuals with amnestic MCI to AD was estimated to be 10-15% per year. This viewpoint has generated extensive research regarding MCI as a precursor to AD (Janoutová et al., 2015). The significant correlation between MCI and AD has prompted researchers to study AD genetic markers within MCI patients (Janoutová et al., 2015).

Neuropsychological assessments also play a role in determining the MCI type in individuals (e.g. amnestic or nonamnestic) by measuring cognitive performance in the prodromal (e.g., early) phases of neurodegenerative diseases (Janoutová et al., 2015). The specific relevance of each piece of prior research is still being examined and explored. All of the current genetic and clinical information mentioned provides valuable information to science and those currently suffering from AD and MCI.

An ethical dilemma has arisen regarding disclosing ApoE genetic risk factors to AD and MCI subjects and has been passionately debated among practicing clinicians. Currently, ApoE is the most robust AD genetic risk factor; however, it typically has not been disclosed to research participants, clinical patients, or their families because of the perceived risks of misunderstandings, safety risks, and discrimination (Green et al., 2009). Many health care providers are unwilling to disclose such information to their research participants, clinical patients, or families because they believe it will cause added harm (Schicktanz et al., 2014). The argument about whether to disclose ApoE genetic risk factors centers on the ethical ideals of autonomy, beneficence, and non-maleficence (APA, 2017). According to Principle A of the American Psychological Association (APA, 2017) Ethical Code, beneficence and non-maleficence requires that psychologists work to benefit the patients/clients they serve while ensuring they do no harm to them. This principle includes safeguarding the welfare and rights of

their patients/clients and, if conflicts arise, resolving them in a way that avoids or minimizes harm. Furthermore, Principle E addresses autonomy, requiring psychologists to respect the dignity and worth of all clients and their right to privacy, confidentiality, and self-determination. APA also notes that special safeguards should also be used to protect those whose vulnerabilities impair their autonomous decision-making (APA, 2017).

Currently, limited research exists to substantiate either side of the ethical argument regarding the harm to clients during ApoE genetic risk disclosure. However, past research with preclinical AD and MCI participants has found no significant short-term harm following genetic risk disclosures (Chao et al., 2008; Green et al., 2009). Previous research has also revealed a significant benefit of ApoE disclosures, as subjects subsequently reported adopting long-term healthy behaviors (Chao et al., 2008). These research studies have generated some insight into the potentially inaccurate past perceptions of the risk of harm regarding disclosure of genetic risk factors to clients. However, the possibility that genetic risk disclosures could be beneficial in some way rather than harmful, requires more careful consideration.

Background of the Problem

The ethical debate on disclosing gene testing results to the public has been longstanding (Ashida et al., 2010). However, the Human Genome Project (HGP) was the beginning of the journey toward genotyping for human biomarkers (Ashida et al., 2010). The HGP was an international research project including the United States, the United Kingdom, France, Germany, Japan, and China, established to determine the DNA sequencing for the human genome, a process which began in 1990 and was completed in 2003. Upon its completion, the

direction of epidemiological research shifted toward identifying genes as risk factors for adverse health events and disease (Kristman & Kreiger, 2008).

As this type of research increased, ethical concerns regarding genetic risk disclosure increased (Kristman & Kreiger, 2008). Ethical issues, such as autonomy, non-maleficence, and beneficence, became the primary focus of the debate about whether to disclose. This debate has encompassed both research and clinical practice settings (Kristman & Krieger, 2008).

Autonomy is an ethical principle where human self-determination is identified and respected (Kristman & Kreiger, 2008). Kristman and Kreiger argued that a patient's genetic test results are a part of their medical records and should be provided so that the patient can make the appropriate decisions and life choices. If genetic test results are not disclosed, then the patient's decisions are not truly autonomous but stem from some level of coercion or manipulation. The main concern becomes how patients can make an informed decision about their future health if they are not given all the information (Kristman & Krieger, 2008).

Non-maleficence is another ethical obligation to minimize or eradicate client harm. The types of harm typically faced in genetic risk disclosures are physical, psychological, and socio-economic (Kristman & Kreiger, 2008). Previously, it was assumed by health care professionals that genetic risk disclosure could cause all three types of harm. However, recent research has called this assumption into question (Krisman & Krieger, 2008).

Finally, there is the ethical issue of beneficence, which extends beyond avoiding harm to intentionally trying to help. In 2008, the REVEAL Study discovered that ApoE genetic risk disclosure generates a motivation to engage in reduced-risk behaviors while increasing treatment adherence (Chao et al., 2008). However, the research in all three ethical areas has been limited

and needs expansion to truly discover whether genetic risk disclosures are ethical violations that harm the public.

Problem Statement and Research Questions

The question arising from past research are as follows:

- Is ApoE genetic risk disclosure ethical, and what outcomes does it potentially generate for those at risk for AD, MCI patients, and preclinical AD patients?

The current literature review seeks to explore this question and discuss ethical dilemmas underlying ApoE genetic risk disclosures for AD and MCI patients.

Purpose of the Literature Review

The purpose of this literature review is to explore and discuss positive and negative health outcomes due to ApoE genetic risk disclosures and the ethical issues surrounding them while providing a current overview regarding ApoE disclosures to MCI and AD patients. In addition, this literature review seeks to generate increased awareness regarding ApoE disclosure to attempt to guide future research and practices in this area. Finally, this literature review analyzes the positive and negative outcomes of ApoE genetic risk disclosures in research and clinical practice, including the more recent method of disclosure provided to the public via telehealth and direct-to-consumer (DTC) genetic testing through online platforms.

Significance of the Literature Review

This literature review seeks to provide increased awareness and clarity regarding ApoE risk disclosure and identify current misperceptions.

Definitions

The terminology used throughout this study is operationally defined in the following glossary:

Alzheimer's disease is a degenerative brain disease that is caused by complex brain changes following cell damage. It leads to dementia symptoms that gradually worsen over time. The most common early symptom of Alzheimer's is trouble remembering new information because the disease typically impacts the part of the brain associated with learning first (AA, 2020a).

Apo lipoprotein E (ApoE) is the protein that combines with fats (lipids) carrying cholesterol and other fats throughout the bloodstream. (National Library of Medicine, 2021)

Amyloid Beta (Aβ) plasma is the result of mutations in the APP, PSEN1, or PSEN2 genes that create neurons in the brain and help neurons adapt. This toxic protein is produced in the brain and can serve as a blood-based biomarker for Alzheimer's disease (National Library of Medicine, 2021).

Amyloid plaques are clumps of the toxic protein amyloid beta that build up in the brain accumulating on the outside of the neuron these clumps may lead to the death of nerve cells and the progressive signs and symptoms of Alzheimer's Disease (National Library of Medicine, 2021).

MCI refers to mild cognitive impairment or an early stage of loss in cognitive abilities or memory in individuals who can still perform their daily activities. MCI individuals may be at an increased risk of AD (AA, 2020b).

Amnestic MCI is a type of MCI that primarily affects the memory of individuals without noticeable effects on their daily life (AA, 2020b).

Nonamnestic MCI is a type of MCI where an individual's thinking abilities are negatively affected, but their memory remains intact and no noticeable impairment on their daily life exists (AA, 2020b).

CHAPTER II: GENETIC TESTING DISCLOSURE AND COUNSELING

Genetic Testing Disclosure

The field of genetics is quickly advancing as new technologies emerge. This constantly shifting reality challenges genetic researchers to reassess potential risks and benefits as genetic sequencing evolves (Prince & Berkman, 2018). These advances offer unlimited opportunities resulting in a wide range of benefits and risks across populations. However, along with these opportunities come four ethical responsibilities including autonomy, confidentiality, privacy, and equity (Andrews et al., 1994). The importance of ongoing ethical assessment of the potential harms and benefits of genetic test use, access, and disclosures should not be underestimated (Prince & Berkman, 2018). Further, in 2017, the company 23andMe gained direct-to-consumer approval from the Food & Drug Administration (FDA) for direct-to-consumer ApoE genetic risk testing (Roberts et al., 2020). As a result, the issue of communicating genetic testing information with patients and their families continues to be at the forefront of ApoE genetic risk testing (Roberts et al., 2020).

Genetic testing can be done for different clinical purposes including predicting risk of disease, identifying carriers and determining both prenatal and clinical diagnosis or prognosis (National Academies of Sciences, Engineering, and Medicine, 2017). At the same time, these differences need to be determined "so that counseling approaches may be matched accordingly" (Wang et al., 2004, p. 1438). Recognizing and addressing these differences may provide the means for customized genetic counseling programs that help increase the significance of genetic information and reduce negative outcomes (Wang et al., 2004). Moreover, disease manifestation, treatability, and social significance can also be genetically analysed. For example, social

significance can involve educating with the purpose of preparing individuals being tested for a disorder as well as the potential impact on their families, support groups, and public so they are able to make truly informed decisions pertaining to genetic testing on both a personal and overall policy level (Andrews et al., 1994). The implications of genetic testing can affect both the individual and society as a whole, therefore the appropriate genetic test and testing practice carries clinical significance (National Academy of Sciences. Engineering, and Medicine, 2017). These issues can involve shared risks with family, using genetic testing in reproductive decisions, and the possibility of genetic results being used to create stigma or discrimination. This information can affect people's ability to define and understand themselves, manage their futures, and impact their perception of self, others, and the world (Andrews et al., 1994). Furthermore, the rapid development of genetic testing technology coupled with unknown health implications of genetic risks, only creates more ethical concerns in health care disparities, data sharing, and reporting of genetic test results (National Academy of Science, Engineering, and Medicine, 2017).

Genetic testing has occurred within various contexts beyond the physician-patient relationship, including public health, clinical research, law enforcement, the military, and insurance companies (Andrews et al., 1994). Historically, these examples include over 4 million newborns tested for metabolic disorders, the collection of fingerprint DNA samples from law enforcement, DNA provided by military members to identify deceased soldiers, and employers/insurance companies' decisions to use genetic testing to exclude individuals from insurance coverage (Andrews et al., 1994). Advancements in human genetics and genomics has been changing the health care system and medical practices with substantial growth and rapidly

advancing technology, along with challenges in genetic testing validity and utility, best practices for genetic testing integration, improved clinical outcomes, and comparing genetic testing drawbacks with benefits (National Academy of Science, Engineering, and Medicine, 2017). Currently, many care models, assessment tools, and other resources are available to assist primary care clinicians in integrating genomic testing data into their practices (Henrikson et al., 2020). Ethical issues have been at the forefront since the HGP began to conduct research and findings were applied to clinical care (Henrikson et al., 2020). In fact, the most frequent question regarding the use of genetic information has been disclosure (Allen et al., 2021). During the first decade of this genetic era (e.g., the Human Genome Project) from 1990 well into the 2000's, the work was considered new, different, and disruptive and was primarily focused on single-gene diseases. Historically, potential harms have included psychosocial harms of anxiety, depression, and distress upon receiving genetic test results, along with genetic discrimination in health, disability and long-term care insurance, and employment. Currently, the generic era has evolved into the genomic era with large panels focused on harms involving false-positive results and unnecessary testing or procedures due to uncertain or incorrect genomic information. Additional potential harm involves false reassurances, specifically regarding direct-to-consumer (DTC) genetic testing services as well as harm to relatives in learning unwanted genetic risk information (Henrikson et al., 2020).

Ethical, legal, and social issues in this area have been studied from 2008 to the present, with the most common topics involving informed consent, sharing data, and privacy issues, especially regarding specific populations' ancestry and socio-economic status and the International Review Board (IRB; Callier et al., 2016). Over time, the most significant growth in

this research has been in the areas of result disclosure and group-level harm (Callier et al., 2016).

In 2005, a research study on participants' behaviors after genetic testing disclosure revealed that individuals testing positive for the ApoE genotype for Alzheimer's were 5.76 more likely to alter their long-term care insurance (Zick et al., 2005). In the case of Alzheimer's, long-term care is usually needed as patients decline. As ApoE genetic risk testing for Alzheimer's becomes more prevalent, the insurance company use of adverse selection (e.g., coverage denials based upon prior genetic test results) regarding long-term care also has potential to increase (Zick et al., 2005).

For instance, in 2018, an empirical legal research approach was used to explore if those who learned their Alzheimer's biomarker status were protected from discrimination regarding insurance policy underwriting or decisions about coverage (Arias et al., 2018). The study compared the National Association of Insurance Commissioners (NAIC) model Long-Term Care Insurance Act with state laws. The analysis method involved four steps: 1) gather, 2) organize, 3) interpret, and 4) apply. The priority of the analysis centered on anti-discrimination protections for preclinical AD and clinical AD biomarker individuals, focusing on protections of employment and health specific to long-term care, life, and disability insurance (Arias et al., 2018).

Research and analysis were conducted in all 50 states and the District of Columbia to ensure consistency (Arias et al., 2018). Researchers found that state laws were consistent with the NAIC Long-Term Care Insurance Model Act regarding pre-existing condition coverage. However, researchers also found that individuals would not be afforded protection from adverse medical underwriting based on their biomarker status. This finding caused researchers to conclude that the current federal and state protections were meaningless to individuals and failed

to prevent long-term care discrimination. Therefore, a re-evaluation of underwriting standards was suggested to help promote access to long-term care benefits so they could be considered along with early risk-detection (Arias et al., 2018).

In addition, a supplemental research study in 2021 analyzed this matter further regarding private payers' long-term insurance coverage, coverage rationale, and guidelines supporting such coverage for ApoE policyholders (Arias et al., 2021). First, the largest private insurance payers in the U.S. were reviewed and the top eight were selected for policy review (e.g., these companies who covered 50% of the U.S. population and 57% of the U.S. population eligible for private insurance). Then, these insurance policies from the eight insurance companies selected were downloaded and analyzed with an inductive coding approach of themes related to long-term care, and genetic risk status was entered into a codebook of coverage rationales. The five themes were 1) genetic risk association, 2) professional guidelines or standards, 3) listing ApoE as having inadequate data to support gene testing, 4) labeling ApoE testing as investigational, and 5) patient management impact. This supplemental research defined "genetic risk association," as the connected risk of AD and related dementia (ADRD) with ApoE genetic test results. The "professional guidelines or standards" was defined as the insurer's rationale for treating or caring for a condition. The "inadequate data" definition was referring to not having sufficient data linking genetic testing to the condition or disease. "Investigational" was defined as when the insurer refers to the genetic testing as medically unnecessary and investigational. "Patient management" was defined as ensuring genetic testing that does not affect clinical management of the patient (Arias et al., 2021).

Seven of the eight payers created policies between 1999 and 2020 specific to ApoE testing, and five of these seven payers did not cover ApoE genetic testing (Arias et al., 2021). Furthermore, two payer policies applied generic pre-authorization criteria to decide if genetic testing is medically necessary to require authorization. All the policies pertaining to standards and guidelines were different but were consistently opposed to ApoE genotyping. Overall, none of the seven private payers covered or would cover genetic testing for ApoE risk of AD, whether clinical or preclinical (Arias et al., 2021).

Based on early research, other than physician-patient settings, ethical guidelines for other settings had not been established or clarified to address autonomy, confidentiality, and privacy. (Andrews et al., 1994). Additional attempts to locate updated guidelines have not been successful. In fact, ethical guidance when handling human genetic information currently only exists through ethically approved research, training for genetic counselors, not specifically for psychologists (Richmond-Rakerd, 2013). Due to this lack of guidance and training, psychologists have relied upon their own ethical guidelines and APA code of conduct (Richmond-Rakerd, 2013). Genetic information can affect entire communities, particularly now with the rapid advances in technology and its use in human genetics. As a result, the importance of consistent and cohesive ethical guidelines regarding genetic information within the psychology field has become crucial (Richmond-Rakerd, 2013).

Disclosure and Counseling Guidelines

In 2020, researchers revisited this topic to determine whether current clinical guidelines adequately addressed disclosure issues regarding dementia or its risks (Alpinar-Sencan & Schicktanz, 2020). Researchers reviewed the clinical guidelines in the U.S., Canada, and

Germany regarding predictive dementia tests and diagnostic disclosure of dementia for MCI patients. The US has a dementia plan, Canada adopted one in 2019, and Germany is still developing one. In the U.S. the dementia guidelines on early detection and accuracy were created and have been updated by the Alzheimer's Association (AA), the National Institute on Aging (NIA), and the U.S. National Institute of Health (NIH). Canada's national dementia strategy and dementia guidelines were created at the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD). In Germany, the current dementia guidelines for physicians and therapists were created by the German Society for Neurology (DGN) and the German Society for Psychiatry and Psychotherapy, Psychosomatics and Neurology (DGPPN; Alpinar-Sencan & Schicktanz, 2020).

This analysis was aimed at revealing potential limitations, providing background regarding ethical implications, and identify methods for proceeding (Alpinar-Sencan & Schicktanz, 2020). These countries were selected as the leaders in the intensive debate and research activities on dementia biomarkers and prevention. These countries also represent a diverse array of healthcare systems, with the US primarily privatized, Germany financed socially, and Canada publicly financed (Alpinar-Sencan & Schicktanz, 2020).

During this review and analysis, the researchers discovered that the US was focused on the biomarkers of Alzheimer's disease and the preclinical stages of dementia to create a society supportive of the early diagnosis of dementia (Alpinar-Sencan & Schicktanz, 2020). The U.S. was found to emphasize counseling; however, among all three countries, no specific guidelines existed regarding disclosing an AD or dementia diagnosis to patients. Only Germany has a specific initiative concerning the disclosure of risk status to individuals. In the U.S., the updated

National Dementia Plan (NDP) listed a failure to disclose a diagnosis to individuals and their families as a problem and as a gap within the existing guidelines. In fact, strategies to address this problem in the U.S. NDP include training an evidence-based guidance for both physicians and care providers. Further, recommendations for MCI individuals at risk of AD included providing patients with information regarding the limits in preventative options, the uncertainty of diagnoses, options for pre- and post-genetic counseling, and the possible need for long-term planning (e.g., advanced directives). In addition, more recent U.S. guidelines regarding MCI individuals emphasized an individual's decision to be tested and recommended preclinical AD disclosures and genetic counseling be conducted face-to-face with the individual and a family member (Alpinar-Sencan & Schicktanz, 2020).

Since 2019, Canada's national strategy has focused on improving care and support, supporting research and innovation, and educating the public through increased awareness and reduction of stigmas (Alpinar-Sencan & Schicktanz, 2020). For example, during the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD), it was recommended that individuals should be informed of their diagnosis with their families. In fact, they determined this disclosure meeting should include information regarding diagnostic uncertainty, support, treatment options, and future life planning. The challenges Canadians identified during this 2019 conference included the heterogeneous level of training for healthcare providers, the lack of support and compassion by providers when disclosing an individual's diagnosis and the reluctance of clinicians to inform those with dementia and their caregivers. In addition, clinicians' challenges include understanding information, the lack of evidence-based guidelines, and identifying the need for more culturally sensitive information and guidelines

(Alpinar-Sencan & Schicktanz, 2020).

In 2016, two leading German medical associations in neurology and psychiatry presented a revised version of clinical guidelines for dementia, the only clinical guidelines in Germany to provide clear recommendations for physicians and therapists (Alpinar-Sencan & Schicktanz, 2020). These guidelines recommend a continuous counseling process for the changing needs of individuals with dementia and their family caregivers. In addition, the guidelines indicate that individuals and caregivers should be provided with information on possible treatment options, support services and assistance, and health/long-term care insurance. Furthermore, the German Medical Association (GMA) currently recommends predictive dementia testing, such as ApoE testing, only for preclinical individuals with a family history of AD to determine their genetic variation while planning for their future, reducing their fears, and assisting them in joining clinical trials. The GMA also made the recommendation to perform genetic testing with appropriate genetic counseling to determine genetic variations for individuals with early-onset AD. However, the GMA does not recommend genetic testing for individuals with subjective complaints or preclinical individuals with no family history of AD due to limited validity testing and the lack of available preventative measures. Given that the progression of AD is still uncertain, ApoE testing and disclosures for this population could result in unnecessary anxiety and this labelling might reduce the benefit of such preventative testing. However, it could also be argued that advanced knowledge of AD could enhance autonomy in the areas of life planning, advanced directives, support resources, medications and even modifications of risk factors. Further, despite the lack of therapeutic options, receiving a diagnosis often provides individuals with relief, especially in cases of dementia as it allows for future planning. Therefore, these

researchers consider detailed counseling after a dementia diagnosis an ethical priority (Alpinar-Sencan & Schicktanz, 2020).

Overall, this research and analysis discovered that the current guidelines did not adequately address the new developments in dementia testing and disclosure (Alpinar-Sencan & Schicktanz, 2020). Specifically, guidelines for counseling, communicating risk, and disclosing results were inadequate. Because the researchers could not identify globally accepted specific risk status disclosure guidelines during their review and analysis, they asserted that risk disclosure guidelines needed to be grounded in empirical studies involving various stakeholders and should include the average person's needs and wishes regarding risk communication (Alpinar-Sencan & Schicktanz, 2020).

Communicating genetic disclosures to patients is especially challenging, as patients can struggle with health literacy and numeracy skills to help them fully understand this information, and their own biases may affect their interpretation (Roberts et al., 2020). To make things more complicated, the healthcare providers are providing disclosure without clear guidelines or training. These healthcare providers may lack the skills to convey the disclosure message or face time limitations in delivering this disclosure information, The matter becomes even more complex for providers when a variant of uncertain significance (VUS) is identified during genetic testing. In this case, the healthcare provider should be recontacted for re-interpreting or re-testing (Roberts et al., 2020).

Roberts et al. (2020) refer healthcare providers to several suggested best practices when communicating genetic testing results for neurodegenerative conditions, by 1) draw upon plain language with clear information about genetic risks and frequencies, 2) utilize visual aids when

explaining any genetic risks, 3) pay close attention to the presentation on genetic risks and the patient's timeline (e.g., lifetime risk vs. next 5 years), 4) omit unessential information regarding the patient's decision process, and 5) review any need to communicate with at-risk relatives for any inherited neurodegenerative conditions (Roberts et al., 2020). During the REVEAL study, pictographs were used to convey how an ApoE risk factor influenced an individual's progression onto AD (Lautenbach et al., 2013). The genetic risk communication process goes beyond accurately conveying results to patients, by explaining the results in a manner clearly understood by the patient and any at-risk relatives (Institute of Medicine et al., 2004).

Diagnosing a neurodegenerative condition like Alzheimer's can have implications far beyond the affected individual. For example, relatives may watch their loved one decline while considering their own genetic risk status (Roberts et al., 2020). Thus, another complication when disclosing genetic risk information for inherited neurodegenerative conditions such as AD involves the confidentiality of an individual's medical information and HIPPA privacy concerns. For example, whether or not consent is obtained to communicate with at-risk relatives, so providers can still assist individuals in sharing their genetic risk information by providing copies of genetic test results, a summary letter from the clinic visit, and educational materials from disease support groups and national organizations (Roberts et al., 2020).

Genetic Testing and Disclosure in Breast Cancer Patients

One area of genetic testing disclosure that has progressed over the years involves the medical practice of identifying and preventing breast cancer through the genetic testing of the BRCA1 and BRCA2 genes (National Breast Cancer Foundation, Inc. [NBCF], 2021). The BRCA or "breast cancer gene" contains two alleles, BRCA1 and BRCA2, which can impact a person's

chances of developing breast cancer. According to the NBCF, the BRCA1 and BRCA2 genes exist in all humans and play a significant role in preventing breast cancer. These two genes help repair DNA breaks that can lead to cancer and uncontrolled tumor growth, known as tumor suppressor genes. If these two genes are mutated or damaged, they become ineffective in repairing DNA breaks and are no longer effective in preventing breast cancer. As a result, individuals with damaged or mutated BRCA genes are more likely to develop breast cancer at a younger age (NBCF, 2021).

Furthermore, carriers of this mutated gene can also pass it to their offspring (NBCF, 2021). Approximately 55%–65% of those with the BRCA1 mutation develop breast cancer before age 70, while approximately 45% of those with the BRCA2 mutation develop breast cancer by age 70. Over time, medical professionals have discovered that early detection can result in successful treatment, including for those with the BRCA1 and BRCA2 mutation. Disclosure of this information has become an integral part in preventing and treating breast cancer (NBCF, 2021).

In 2008, a study was conducted involving 155 women, 38 of whom were positive for the BRCA1 or BRCA2 gene mutation (Beran et al., 2008). The inclusion criteria required participants to be 18 years old or older and have a history of breast/ovarian cancer within participants families or 10% chance of carrying the BRCA mutation 1 or 2. Further those who received the BRCA testing between April of 1999 and March of 2004 were eligible for this study. Exclusion criteria included those who tested positive for an unknown significant variable and participants who were non-compliant in completing follow-up assessments. At the first appointment, the eligible participants received a risk assessment and genetic counseling visit and

completed a consent and a depression measure. The second appointment involved participants having their blood drawn for genetic testing and completing baseline measures. During the third appointment, participants received their test results with a genetic counselor. Participants were mailed follow-up questionnaires at 1, 6, and 12 months, which they completed and returned by mail (Beran et al., 2008).

The measures used to assess any possible depression, anxiety, or negative affect included the Center for Epidemiologic Studies–Depression Scale (CES-D; Radloff, 1977), the Positive and Negative Affect Scales (PANAS; Watson et al., 1988), and the State-Trait Anxiety Inventory (SAI; Spielberger et al., 1970). Disclosure of BRCA testing information resulted in significantly more depressive symptoms, negative mood, and cancer-specific distress for mutation carriers versus non-mutation carriers at 1 and 6 months. However, at 12 months, the carriers' moods returned to baseline, with their depressive symptoms decreasing. The researchers concluded that although the mutation carriers' general stress and cancer-specific distress increased initially (from 1 to 12 months), after a year, the distress remitted (Beran et al., 2008).

In 2012, another study explored the psychological effects of disclosure regarding the BRCA1 and BRCA2 genetic mutation (Bosch et al., 2012). This study included 364 participants whose distress and psychological well-being were assessed at 3 months and 1 year after disclosure of their BRCA1 or 2 results. Their distress, depression, and anxiety were measured utilizing self-report questionnaires regarding their perceived risk of cancer and their concerns about genetic testing using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). The HADS includes 14 items with two subscales (anxiety and depression), including a 4-point scale (0–3), typically used to measure psychological distress for oncology

patients, with scores > 10 indicating probable distress and scores > 7 indicating possible distress (Mella et al., 2017). The disclosure of the BRCA genetic testing results revealed no short or long-term influence on anxiety and depression levels for those identified as mutation carriers (Bosch et al., 2012).

In 2014, researchers reviewed the psychological outcomes for individuals receiving disclosure and genetic counseling regarding BRCA mutations in person (IPGC) versus telehealth genetic counseling (TGC; Kinney et al., 2014). Between August 2010 through September 2012, participants were recruited into a randomized equivalency/noninferiority trial aimed at comparing in-person genetic counseling to telephone genetic counseling regarding BRCA 1/2 test results. This study involved 988 participants who were evaluated for cancer-specific distress and anxiety. The measures used included the Brief Symptom Inventory 18 (BSI-18; Derogatis, 2000), the Impact Event Scale (IES; Horowitz et al., 1979), the Decisional Conflict Sale (DCS; O'Connor, 1995), and the Decision Regret Scale (DRS; O'Connor, 2003). Psychological outcomes were evaluated at baseline, 1 week after pre-test counseling, 1 week after post-test counseling, and 6 months after the last counseling session. The study revealed that the outcomes for both the IPCG and TGC groups followed a similar course, with higher initial distress decreasing to baseline over time. In addition to a pattern of decreasing distress, the authors concluded that genetic counseling can be effectively delivered using innovative delivery models, which may be crucial to ensure all individuals receive their results in a timely manner moving forward (Kinney et al., 2014).

In 2017, a short-term observational study was conducted for BRCA mutation carriers to explore the range of emotions experienced by individuals after receiving their risk-disclosure

status (Mella et al., 2017). This study involved 91 participants with an average age of 48 (range 23–75 years old). More than half of these participants were married or cohabitating (74%), and 80.2% confirmed having at least one child. Participants' education level was at least 8 years (48.3%), with 51.7% having more. Over half (65.9%) of the participants were employed, with only 34.1% identifying as students, homemakers, unemployed, or retired (Mella et al., 2017).

The study participants received their materials via mail 1 month after receiving their genetic test results. Before the genetic test disclosure, participants were informed about the genes under investigation and all the potential outcomes, including percentages of breast and ovarian cancers caused by genetic mutation and testing benefits (Mella et al., 2017). During genetic disclosure, each participant was provided with the results, their meaning, and possible limitations (including negative results). Participants with positive results were briefed on the importance of sharing their information with family and provided guidance for prevention and appropriate interventions (Mella et al., 2017).

One month after the genetic test result disclosure, participants received study- materials in the mail which included the following: 1) the HADS (Zigmond & Snaith, 1983), 2) the Profile of Mood States (POMS; McNair et al., 1971), 3) ad hoc emotional thermometers to rate feelings, 4) a form to collect socio-demographic and clinical data, and 5) a prepaid envelope for returning materials (Mella et al., 2017). The POMS assessment is typically used to assess mood states and includes 58 items with five negative scales (i.e., Tension-Anxiety, Depression-Dejection, Anger-Hostility, Fatigue-Inertia, Confusion-Bewilderment) and one positive scale (i.e., Vigor-Activity). This assessment requires participants to rate each item on a 5-point scale (0–4), with higher values equating to higher mood state intensity. The ad hoc emotional thermometers asked

participants to rate the intensity of their emotions on a 0-10 point scale. They measured the intensity of anger, anxiety, concern, confidence, confusion, discomfort, fear, guilt, sadness, and serenity. (Mella et al., 2017).

The POMS findings revealed significantly more anxiety (2 out of 5 participants) than depression (1 out of 4 participants; Mella et al., 2017). The measured mood states indicated that 1 out of 4 participants' anger-hostility exceeded the norm, while 3 out of 10 endorsed significant fatigue-inertia. Of the six mood states observed, confusion was the lowest ($M = 48.5$), and fatigue was the highest ($M = 52.3$). Of the 10 emotional states measured with the thermometer, the most intense emotions endorsed by the participants were confidence and serenity, possibly due to genetic counseling. The researchers in this study concluded that genetic counseling can be helpful and should cover a wide range of psychological-emotional areas (Mella et al., 2017).

In 2020, researchers explored diversity issues regarding BRCA testing disclosure and genetic counseling (Conley et al., 2020). Prior research in this area has been understudied among black women regarding their disclosure of genetic testing to family members or others. This study was focused on fulling this existing gap. This study involved 149 African American women diagnosed with breast cancer, recruited through the Florida Cancer Data System (FCDS), who received free genetic testing. Inclusion criteria were as follows: 1) Black women, 2) living in Florida when diagnosed with invasive breast cancer, 3) diagnosed at or below age 50, 4) diagnosed between 2009–2012, 5) alive at the time of recruitment, and 6) able to speak English.

Participants completed informed consent, a medical records release, study questionnaires, free genetic counseling, and a DNA saliva test (Conley et al., 2020). The study questionnaires included information pertaining to any risk management behaviors, psychological functioning

(e.g., cancer distress, emotional health), social functioning (e.g., communication of test results to others) prior to genetic testing and 1 year after test results disclosure. After genetic disclosure and counseling, participants were asked to complete the follow-up questionnaire at 1 year. These researchers investigated to whom these symptomatic participants disclosed their test results over time (Conley et al., 2020).

The study discovered that 77% of the participants disclosed their results to a family member; however, the BRCA1/2 positive participants had a significantly ($p < .001$) higher disclosure rate to female than male family members (Conley et al., 2020). Furthermore, these BRCA1/2 positive participants were also less likely to disclose results to their daughters, revealing a need for more education on the benefits of genetic testing for family members (Conley et al., 2020).

In summary, the first decade of the Human Genome Project (e.g., 1990-2000's) was focused on the single-gene conditions, including the psychosocial harms of anxiety, depression, and distress upon receipt of genetic test results and discrimination concerns surrounding both insurance coverage and employment (Henrikson et al., 2020). Eventually, epidemiological research began to shift towards genetic risk factors (e.g., biomarkers) for adverse health events and disease (Kristman & Krieger, 2008). As this research increased, so did ethical concerns regarding genetic disclosures and their connection to autonomy, non-maleficence, and beneficence (Kristman & Krieger, 2008). Since 2008, relevant ethical, legal and social issues have been studied and usually involved informed consent, data sharing, and privacy (Callier et al., 2016). The most significant growth within genetic research continued to be disclosure and group harm (Callier et al., 2016). Technology advances have kept genetic risk disclosure at the

forefront of the harm versus benefit ethical debate (Roberts et al., 2020; Prince & Berkman, 2018). Researchers have since realized the importance of recognizing and identifying the clinical purpose for genetic disclosure when determining a genetic counseling approach (National Academics of Science, Engineering, & Medicine, 2017; Wang et al., 2004). They suggested that a customized genetic counseling approach could increase the significance of genetic information and reduce negative outcomes overall (National Academic of Science, Engineering & Medicine, 2017).

In 2005, a positive outcome discovered by researchers was that ApoE positive participants were five times more likely to modify their long-term care insurance; however, they also realized that adverse selection and denial of long-term care by insurance companies was possible (Zick et al., 2005). These discoveries resulted in additional research studies through the present, confirming a lack of federal or state law protections regarding long-term care (Arias et al., 2018). Further work discovered that 5 of 7 insurance companies did not cover genetic testing and 0 of 7 of these same companies covered ApoE genetic testing for AD (Arias et al., 2021).

More recently, additional research was re-explored pertaining to the clinician guidelines available regarding genetic counseling, communicating risks, and genetic disclosure to individuals (Alpinar-Sencan & Schicktanz, 2020). The guidelines were found to be inadequate and in need of grounding in empirical studies that address the average person's communication needs and wishes (Alpinar-Sencan & Schicktanz, 2020). In this regard, researchers realized that genetic risk communication goes beyond accuracy and needs to be clearly understood by the patient and any relative (Institute of Medicine et al., 2004). Subsequently, additional research

was performed to determine best practices when communicating genetic disclosures to patients (Roberts et al., 2020).

Finally, genetic testing disclosure regarding breast cancer was reviewed from 2008 forward to discover what approaches yielded positive and negative outcomes for patients. Overall, these breast cancer studies revealed that more detailed communication and education regarding genetic results and testing, yielded more positive outcomes for participants (Beran et al., 2008; Bosch et al., 2012, Kinney et al., 2014; Mella et al., 2017). An additional research study in 2020 discovered that African American women tended to disclose their positive genetic testing results to a female family member, revealing a need for educating family members on genetic testing benefits as well (Conley et al., 2020).

Alzheimer's disease (AD) and mild cognitive impairment (MCI) are two of this century's most significant healthcare challenges, with 40 million people currently suffering from the diseases. In fact, progressive AD and MCI is expected to double every 20 years until 2050 (AA, 2020a). ApoE is the most robust AD genetic risk factor, but typically has not been disclosed to research participants, clinical patients, or their families because of the perceived risks of misunderstandings, safety risks, and discrimination (Green et al., 2009). Many health care providers are unwilling to disclose such genetic information to their research participants, clinical patients, or families because they believe it will cause added harm (Schicktanz et al., 2014). Past research has not found significant short-term harm after genetic risk disclosures, but instead revealed a significant benefit of participants adopting long-term healthy behaviors (Chao et al., 2008; Green et al., 2009). However, the possibility that genetic risk disclosures could be beneficial in some way rather than harmful requires more in depth and careful analysis.

CHAPTER III: THE IMPACT OF APOE GENETIC RISK DISCLOSURE AND COUNSELING

Genetic test results impact their recipients both psychologically and behaviorally (Roberts et al., 2020). This impact can be even more intense for those receiving test results regarding neurodegenerative disorders, as they typically involve someone learning about the almost-certain likelihood of a feared disease such as Alzheimer's (Roberts et al., 2020).

Over the last decade, several research studies have found that psychological distress in response to predictive testing is generally mild and transient for those who undergo testing, a finding replicated in numerous studies and observed across multiple other disease contexts, from hereditary cancer syndromes to Alzheimer's disease (Crozier et al., 2015; Heshka et al., 2008). Such findings suggest that the likelihood and extent of psychological harm from genetic testing—even for fatal and incurable diseases—is less than was initially feared. Nevertheless, this body of research has several notable limitations: 1) the use of skewed participant samples lacking in diversity concerning race and socio-economic status, 2) the use of traditional in-person genetic counseling models that limit the generalizability of results to other formats (e.g., DTC genetic testing), and 3) an overreliance on general depression and anxiety scales as primary outcome measures (Roberts et al., 2020).

Historically, ApoE genetic risk testing for Alzheimer's disease has been performed for years without any disclosure to the research participants or patients (Bemelmans et al., 2016). The rationale has always focused on AD as an incurable degenerative disease without a positive prognosis. However, the potential impact of disclosure has been examined in more detail recently. This review of the literature regarding ApoE genetic risk disclosure outcomes and

behaviors includes early studies from 2005, that were most focused on preclinical subjects with a family history of AD and/or MCI, not symptomatic clinical subjects.

In 2005, the first randomized controlled research study was performed to examine the psychological and behavioral impact of ApoE disclosures for preclinical AD patients (Roberts et al., 2005); this study was identified as the Risk Evaluation and Education for Alzheimer's disease (REVEAL) study. This study was created to analyze what impact disclosure of ApoE risk for AD would have on individuals. Participants were children of AD diagnosed or autopsy confirmed individuals. They were either self-referred (n = 115) or contacted through a family member's connection to AD research (n = 47). This multi-site randomized clinical trial included 162 participants with a mean age of 53, 72% female, and 94% White, with a mean education of 16.7 years. Participants were randomized into one of two groups: an intervention group (n = 111) or a control group (n = 51). The intervention group received counseling and risk assessment according to their family history of AD, gender, and ApoE genotype, while the control group was excluded from the ApoE genotype disclosure. The individual risk disclosure sessions lasted 30–60 minutes, covering risk, providing support, and answering questions (Roberts et al., 2005).

During this study, participants were initially provided with educational sessions, and those interested continued to the blood draw portion of the study to determine ApoE genotyping (Roberts et al., 2005). The intervention group was ultimately split into two sub-groups: ApoE-ε4 positive (n = 53) and Apoe-ε4 negative (n = 58; Roberts et al., 2005).

Assessments for anxiety, depression, and distress were given at baseline, 6 weeks, 6 months, and 1 year after risk disclosure. The assessments utilized included the Beck Anxiety Inventory (BAI; Beck et al., 1988), the Center for Epidemiological Studies – Depression Scale

(CES-D; Radloff, 1977), and the IES (Horowitz et al., 1979).

Initial data analysis indicated that risk assessment and Apoe-ε4 disclosure did not adversely affect participants' psychological well-being (Roberts et al., 2005). In fact, 90% of participants reported the same or lower anxiety levels regarding AD compared to their baseline anxiety. Furthermore, at 6 weeks, 6 months, and 1 year, there were no significant post-test differences in depression or anxiety symptoms among all three groups. Further, the few participants who did report symptoms of depression or anxiety post-disclosure were interviewed by genetic counselors and these symptoms were found to be due to external stressors outside their disclosures. Instead, the study discovered that most participants experienced lower anxiety levels about AD following their risk disclosure (Roberts et al., 2005).

Although this study had an adequate number of participants, dividing the intervention groups may have impacted power. The participants were not diverse in gender, ethnicity, or race, and the use of only self-report assessments could have introduced additional response biases. Therefore, the selection process for future research should be designed to include a more diverse and accurate representation of the general population, collateral information, as well as some increase in group sizes where possible.

Research specific to the impact of disclosing ApoE genetic risk to individuals has continued to evolve. Although it began in 2005 with the REVEAL study, this research was further expanded that same year to analyze participants' perceptions of risk for AD. This additional research used a subset of the 2005 REVEAL participants and used an experimental randomized controlled design. This subset involved 66 participants divided into two groups who received the identical 29% lifetime risk estimate of developing AD (LaRusse et al., 2005). The

first group included women selected based on family history and gender (n = 36). The second group of women was selected based on ApoE-ε3/ε3 genotype, gender, and family history (n = 30).

The structure of this design involved one independent variable (ApoE genetic test results), one continuous variable (the 29% lifetime AD risk estimate), and one dependent variable (the level of participants' perceived AD risk). The genotype participant group (n = 30) received this 29% lifetime AD risk estimate along with their ApoE genetic test results, while the family history participant group (n = 36) only received the 29% lifetime AD risk estimate.

All participants were assessed before and after risk disclosure. The assessments given before disclosure included 1) the Repeatable Battery for the Assessment of Neuropsychological Assessment (RBANS; Randolph et al., 1998), 2) the Mini-Mental Status Exam (MMSE, Folstein et al., 1975), 3) the Wide Range Achievement Test-3rd (WRAT-3; Snelbaker et al., 2001), 4) the CES-D (Radloff, 1977), 5) the BAI (Beck et al., 1988), and 6) the PANAS (Watson et al., 1988). The assessments administered to participants after risk disclosure were given at 6 weeks, 6 months, and 1 year using 1) the CES-D (Radloff, 1977), 2) the BAI (Beck et al., 1988), 3) the PANAS (Watson et al., 1988), 4) the Future Anxiety Scale (FAS; Zaleski, 1996), and 5) the IES (Horowitz et al., 1979; LaRusse et al., 2005).

The analysis done at 6 weeks revealed that the participants who were provided with their risk assessment and ApoE results (i.e., genotype group) perceived their AD risk as lower than participants not provided with their genetic risk (i.e., family history group), at a ratio of 73% (genotype group) versus 25% (family history group; p = 0.0001; LaRusse et al., 2005). The genotype group also reported 67% lower anxiety for AD than at baseline versus the family

history group's anxiety, which was only 26% lower than at baseline ($p = 0.01$). Furthermore, the data confirmed a more positive event impact at 80% for the genotype group but only a 36% positive impact for the family history group ($p = 0.0001$). The genotype group was also less likely to believe they would develop AD at 13%, while 36% of the family history group believed they would develop AD ($p = 0.05$). Finally, the genotype group was more likely to report an uncertainty of developing AD: 63% (genotype) vs. 9% (family history; $p = 0.0001$; LaRusse et al., 2005). Data analysis was also done at 6 months and 12 months, but participants response pattern was unchanged from the 6-week data responses; therefore, the researchers only reported the 6 weeks analysis. The data led researchers to conclude that negative emotional perceptions regarding AD were greater when participants were provided with less risk information (e.g., only their family history risk percentage). This initial research challenged the previous perception that ApoE risk disclosure did more harm than good. In addition to the overall limitations of the REVEAL study, this subset sample involved only females, further limiting generalizability.

Another 2005 supplemental study was performed with participants from the previous REVEAL study regarding Apoe-ε4 risk disclosure (Zick et al., 2005). The researchers were interested in the relationship between Apoe-ε4 risk disclosure and insurance purchasing behavior outcomes. This quasi-experimental design involved 148 participants from the original REVEAL study ($N = 162$) placed into three groups—a control group with no Apoe-ε4 risk disclosure ($n = 46$) and two other experimental groups—a group of participants who learned about their negative Apoe-ε4 risk ($n = 54$) and a final group of participants who learned about their positive Apoe-ε4 risk ($n = 48$; Zick et al., 2005).

The design structure was a multivariate logit model examining the impact of Apoe-ε4 risk disclosure status on changes to insurance while controlling for confounding factors (e.g., marital status, age, sex, and education; Zick et al., 2005). The dependent variables were the non-disclosure and any negative or positive Apoe-ε4 risk disclosure status, with an independent variable regarding any changes to insurance post-disclosure. Questions regarding changes were asked during the post-disclosure interviews at 6 weeks, 6 months, and 1 year. The questions included whether the participants were making or planning to change their health, life, disability, and long-term care insurance following the risk disclosure (Zick et al., 2005).

Regarding health, life, and disability insurance, no significant changes post-disclosure were discovered (Zick et al., 2005). Research participants who tested positive for the ε4 allele were only moderately more likely to consider changing their life insurance coverage ($p \leq 0.10$; Zick et al., 2005). However, the participants with a positive Apoe-ε4 risk disclosure status were more likely to report making changes in their long-term care insurance ($p = 0.05$). This result remained the same for the positive Apoe-ε4 risk disclosure participants, even after controlling for the covariates of marital status, age, sex, education, concern about developing Alzheimer's disease, past/present experience as an Alzheimer's caregiver, and prior insurance coverage (Zick et al., 2005).

The results revealed that approximately 17% of the Apoe-ε4-positive participants changed their long-term care insurance 1 year after disclosure. In comparison, approximately 2% of the Apoe-ε4 negative participants and 4% who received no Apoe-ε4 disclosure changed their long-term care insurance at 1 year (Zick et al., 2005). The overall increase in long-term care insurance within the total sample went from 19.8% at baseline to 27% 1 year after disclosure.

When controlling for covariates, these researchers found that Apoe-ε4-positive participants were 5.76 times more likely than non-disclosure participants to change their long-term care insurance within 1 year of disclosure. In this study, participants receiving the Apoe-ε4-positive risk disclosure displayed more proactive behaviors such as taking steps toward their future healthcare. In this regard, the additional disclosure of information appears to have yielded a positive outcome for the participants (Zick et al., 2005).

However, the researchers in this study also discussed that this type of proactive healthcare behavior could negatively impact long-term insurance care viability and pricing (Zick et al., 2005). They mentioned the potential for insurance companies to decide to implement adverse selection tactics that could include denying coverage to Apoe-ε4-positive individuals. When one considers that Alzheimer's disease is responsible for the longest, most common, and most costly long-term care insurance claims, the potential for adverse selection is a valid concern. Researchers in this study also noted that this fear of adverse selection might cause consumers to decline Apoe-ε4 genetic testing (Zick et al., 2005).

Lawmakers have since recognized this potential for harm from genetic testing and ultimately passed the Genetic Information Nondiscrimination Act (GINA), which became effective on May 21, 2009, to protect consumers from discrimination (National Library of Medicine, 2021). Unfortunately, exceptions exist to this law's protection because while consumers' health insurance coverage is protected, life, disability, and long-term care insurance are not (Arias et al., 2018). AD patients typically require some type of long-term insurance coverage and may even need to use disability insurance if they are diagnosed with early-onset AD. Furthermore, their life insurance may be necessary to provide for their family after passing

away from AD (Arias et al., 2018). As a result, the American Psychological Association's code of ethical guidelines on avoiding harm, Standard 3.04, requires that clinicians discuss such potential negative outcomes with the patient before any Apoe-ε4 testing or disclosure, and inquire about the patient's disability, long-term, and life insurance coverage before testing (APA, 2017, 3.04).

Another study based on the REVEAL study was performed in 2008 to examine whether ApoE genetic risk disclosures in preclinical AD participants yielded any change in health behaviors (Chao et al., 2008). The participants included 162 subjects randomized initially with 15 participants dropping out during the 1-year follow-up period, resulting in a final analysis of 147 subjects.

This experimental randomized controlled design involved two groups: the intervention group received the ApoE-ε4 risk disclosure while the control group did not (Chao et al., 2008). Before randomization, all participants were educated on the ApoE-ε4 allele risk factor as neither necessary nor sufficient to cause AD. Participants were also informed there were no preventative measures for AD but were given information regarding the available therapies being investigated for possible prevention from this disease (e.g., vitamin E, anti-inflammatory medications, hormone replacement, cholesterol-lowering drugs, and mental stimulation).

The design structure involved a logistic regression comparison of changes in AD-specific behaviors among the intervention disclosure group, including both positive ApoE-ε4 and negative ApoE-ε4 risk participants (Chao et al., 2008). A control group received no disclosure information, only a risk estimate based on their demographic information and family history. In addition to disclosure information, the researchers also collected information on the subjects' demographics, family, and medical history, including 1) age, 2) sex, 3) education, 4) family

history, 5) diabetes mellitus, 6) heart disease, 7) hypertension, 8) hypercholesterolemia, 9) thyroid disease, 10) cancer, and 11) osteoporosis. The researchers provided the intervention subjects with their ApoE-ε4 risk status and a lifetime risk estimate based on each subject's ApoE-ε4 risk status, sex, and family history, while the control group only received a lifetime risk estimate based on each subject's sex and family history (Chao et al., 2008).

The researchers focused their analysis on their hypothesis that subjects who were positive ApoE-ε4 would be more likely to change AD health behaviors compared with negative ApoE-ε4 and control subjects (Chao et al., 2008). One year after the participants' disclosure, they were asked three questions about their AD preventative health behaviors regarding changes in diet, exercise, and medications or vitamins. Participants were asked to explain these changes during an open-ended interview (Chao et al., 2008).

The study discovered that positive ApoE-ε4 participants were significantly more likely than either the negative ApoE-ε4 group (52% vs. 24%, $p = 0.003$) or the control group (52% vs. 30%, $p = 0.03$) to make changes in their AD preventative health behaviors (Chao et al., 2008). The main change positive ApoE-ε4 participants endorsed was medications or vitamins to help prevent AD, with vitamin E being the most common. The positive ApoE-ε4 participants were 2.73 times more likely to endorse changes in AD prevention health behaviors than negative ApoE-ε4 participants, even after researchers adjusted for the previously mentioned variables of demographics and medical history conditions. Furthermore, during post-hoc analysis, researchers utilized the lifetime risk estimate in place of the ApoE-ε4 risk status and found a 5% increase in the odds that participants would endorse AD-specific behavior changes for every 1% increase in lifetime risk ($p < 0.005$). During logistical regression analysis of the two variables (i.e., AD risk

status and lifetime risk estimate), neither could independently predict changes in AD prevention health behaviors, resulting in the conclusion that both variables have some correlation to one another and the results of health behavior changes (Chao et al., 2008).

This collinearity was confirmed by using tolerance statistics and fit of models, including ApoE genotype only, lifetime risk only, and both variables together. The researchers co2nfirmed collinearity with the receiver operating characteristic statistic (ROC). The findings revealed the following: ROC = 0.729 for the model with the ApoE genotype, ROC = 0.728 for the model with a lifetime risk estimate, and ROC = 0.727 for the model with both variables (Chao et al., 2008). This study's results led the researchers to conclude that disclosure of an individual's AD risk motivated them to engage in behaviors to reduce risk in some way, even if the effectiveness of their behaviors was unknown (Chao et al., 2008).

In 2009, secondary data analysis was performed on the REVEAL study (REVEAL II). This additional research analysis investigated the psychological impact and behavioral outcomes of ApoE genetic testing for adult children of living or deceased individuals with AD whose onset occurred after 60 years old (Ashida et al., 2009). The researchers specifically focused on communicating test results to others and how demographics and AD beliefs affected any communication. The study was conducted at several universities located in the eastern United States with participants recruited by ads, referrals, research registries, word of mouth, and local presentations, with 19% of participants being African American. All participants spoke English and were screened at baseline to exclude those with cognitive impairments or clinically significant depression or anxiety, resulting in 271 participants. Participants received genetic counseling, education, and ApoE testing after this baseline screening. The participants' ApoE test

results and the lifetime risk of AD were disclosed in one of two ways: 1) extended, which involved three in-person visits or 2) condensed, which included two in-person visits and an educational brochure. All in-person visits were conducted by either a genetic counselor or a physician. After the baseline screener, assessments were administered at 6 weeks, 6 months, and 1 year after ApoE testing disclosures. Prior to being provided with educational information and genetic disclosure information, research participants perceived their risk of developing AD at 51% (Ashida et al., 2009).

The communication assessments given involved two questions about sharing their results with others: 1) Have you told anyone the results of your ApoE genetic test? and 2) Who did you tell about the results of your ApoE genetic test? (Ashida et al., 2009). Participants were also asked to rate the benefits versus drawbacks of ApoE genetic testing on a Likert scale (1–5), with 1 being *not at all* and 5 being *extremely*. The following belief areas were also assessed using Likert scales:1) casual AD beliefs, 2) AD treatment optimism, 3) AD concern, 4) perceived risk of AD, and 5) demographic characteristics (e.g., education, gender, race, marital status) and AD. These ratings were then averaged together for analysis. Only the 6 weeks results were discussed during the researchers' analysis. Five logistical regression models were utilized for each of the above outcome variables to determine their association with the data regarding communication of ApoE tests results (Ashida et al., 2009).

The researchers' results revealed that over 80% of the 271 total participants ages 33 to 86 reported telling someone about their ApoE test results, with half of these participants (57%) under 60 years old (Ashida et al., 2009). Of the 80% who communicated their ApoE test results, 64% told their family members, 35% told their friends, and 12% told their health professionals.

Moreover, 51% of all participants who were married or with partners communicated their results to their significant others. (Ashida et al., 2009).

When participants perceived lower levels of risks of AD combined with firm beliefs regarding the genetics of developing AD, they were more likely to communicate their results to someone ($p < .01$; Ashida et al., 2009). Furthermore, the participants with a higher perceived optimism regarding an AD cure revealed a significantly higher chance of communicating ApoE results with their family ($p = .05$), spouses ($p = .02$), partners ($p = .02$), friends ($p < .01$), or health professionals ($p = .01$. Participants who perceived lower levels of drawbacks in ApoE testing were significantly more likely to communicate their results with friends. Female participants were two times more likely than males to communicate their ApoE results with their families ($p = .02$). Participants with higher education, of White ethnicity, or who were over 60 were all more likely to communicate ApoE results with friends or family ($p = .02$). Finally, participants who received the condensed disclosure protocol versus the extended disclosure protocol were significantly more likely to share ApoE results with health professionals ($p < .01$). Interestingly, ApoE test results alone were not significantly associated with whether participants communicated results (Ashida et al., 2009).

The conclusions reached during this study indicated that ApoE test results were shared with others, especially family, by the majority of research participants but are sometimes shared with other individuals (Ashida et al., 2009). It was also determined that additional research may provide clarity pertaining to the factors connected with this type of communication. Ultimately, the researchers concluded that no matter what the reasoning, communication of ApoE test results and other genetic test results impacts more than the participants; it can also impact their families.

Researchers also noted that additional research similar to this study may help determine the clinical utility of genetic testing (Ashida et al., 2009). Further, additional research in ApoE test results communication is needed to assess if any added interventions are necessary to examine communication by test result recipients and explore the effects of doing so. This impact may not always be a positive thing, as disclosure may "force" information on family members who may not want it. The participants may not have considered these nuances before communicating these genetic disclosures. Finally, better assessment measures need to be implemented beyond a series of Likert scales.

In 2010, further additional research analysis examined the psychological impact and behavioral outcomes of ApoE genetic testing for those unaffected by AD and those who had one first-degree relative affected by this disease (Ashida et al., 2010). The data analysis was obtained from the second REVEAL study: REVEAL II (Ashida et al., 2010). The average age of participants in the REVEAL II (2010) study was 58.1 years old with 16.1 years of education, 29.4% were male, 80.7% were white, and 61.3% were married (Ashida et al., 2010).

The initial participants were screened to exclude anyone cognitively impaired or struggling with clinically significant depression or anxiety, resulting in 269 participants (Ashida et al., 2010). Once baseline assessments were completed, participants received education and counseling regarding genetics and ApoE testing. The ApoE test results and estimated lifetime risk of AD were disclosed in either an extended or condensed protocol by a genetic counselor or physician. The extended protocol involved in-person education, individual counseling (76 minutes long), neuropsychological and psychological screening, and a blood draw. The condensed protocol included receiving an educational brochure by mail, a question-and-answer

session, individual counseling (33 minutes long), neuropsychological and psychological screening, and a blood draw (Ashida et al., 2010).

All participants were assessed before and after their risk disclosure, with follow-up assessments administered at 6 weeks, 6 months, and 1 year after the initial risk disclosure. The assessments given included 1) the CES-D (Radloff, 1977), 2) the BAI (Beck et al., 1988), 3) the Impact of Genetic Testing for Alzheimer's Disease (IGT-AD; Chung et al., 2009), and 4) the Multidimensional Impact of Cancer Risk Assessment Questionnaire (MICRA; Cella et al., 2002). The final assessment utilized was an additional measure to determine perceived risk. This measure contained five items adopted from a prior study, with three items measuring participants' levels of concern for developing AD and two items measuring participants' beliefs that they would develop AD as the worst disease. Participants' levels of perceived risk were calculated on a scale from 0% to 100% (Ashida et al., 2010).

There were several outcomes measured in this study, including participants' 1) communication to others about ApoE test results, 2) rating of the benefits and drawbacks of genetic testing for AD, 3) perceived causes of AD, 4) AD treatment optimism, 5) AD concern, 6) perceived risk of developing AD, and 7) demographic characteristics (Ashida et al., 2010).

During data analysis, the researchers used three multiple regression models: 1) depression (CES-D), 2) anxiety (BAI), and 3) the impact of AD testing (IGT-AD; Ashida et al., 2010). Each model was controlled for race, marital status, genotype, and type of disclosure protocol. The models for depression and anxiety were also controlled for their baseline levels. Since none of the participants had prior genetic testing, their baseline levels were set to the IGT-AD model. In addition to symptoms of depression, anxiety, and distress, the researchers analyzed four variables

within these models: perceived AD risk, concern about AD, beliefs regarding AD genetics/heredity, and lifestyle factors. Baseline data was compared in each model with significant variables and for analysis (Ashida et al., 2010).

Research results from baseline through 12 months revealed a decrease in depression from an average score of 24 to 14, with 55% of all participants reporting no change or a decrease in depression symptoms (Ashida et al., 2010). Over the 12-month follow-up period only 9%, or 24 of all the participants, reported scores above the clinical cutoff point. However, 21 of these 24 participants reported depression scores below the baseline cutoff initially. All the participants' anxiety scores revealed that only 33% showed increased anxiety symptoms at 1-year post-disclosure. Furthermore, during the 12-month assessment period, all participants' distress scores were only 1.32 on a scale of 0–17 (Ashida et al., 2010).

The descriptive statistics measuring AD perceptions of participants analyzed relationships between the following beliefs: perceived risk of AD, concerns regarding AD, the genetic cause of AD, and sharing results with friends (Ashida et al., 2010). At baseline, increased depression was associated with a higher perceived risk of AD ($b = 0.22$, $p < 0.01$) and a lower level of AD genetic cause attribution ($b = –0.16$, $p < 0.01$). At 6 weeks post-disclosure, there was a short-term increase in participants' AD concerns ($b = 0.20$, $p < 0.01$). At the 12-month post-disclosure, a decrease in participants' depression was associated with their sharing of ApoE test results with health professionals ($b = 0.10$, $p < 0.05$). All of the increases mentioned above occurred prior to the 12-month post-disclosure analysis which was outside the researcher's design model; however, they did involve high scores on the IGT-AD (Ashida et al., 2010).

Furthermore, the participants' 12-month AD concerns increase was associated with increased anxiety ($b = 0.20$, $p < 0.01$), but participant sharing of test results with friends was associated with decreased anxiety ($b = 0.17$, $p < 0.01$; Ashida et al., 2010). Also participants' IGT-AD scores and AD concerns revealed an increase from baseline ($b = 0.19$, $p < 0.04$ to $b = 0.18$, $p < 0.02$). At 12 months, participants' increased perceived risk of AD was associated with higher levels of distress about AD testing ($b = 0.17$, $p < 0.04$; Ashida et al., 2010).

The researchers discovered that changes in beliefs and perceptions about AD *after* receiving genetic test results could have some influence on one's ability to adapt psychologically over time (Ashida et al., 2010). Although these participants reported overall lower symptoms of depression, anxiety, and distress regarding ApoE testing results, the data revealed some connections between levels of depression, anxiety, and distress and prior perceptions regarding AD. Whether this ability to adapt psychologically was negatively or positively influenced could not be determined from this initial research alone. However, these researchers did determine the participants' higher levels of perceived risk *before* ApoE testing also revealed a higher perceived risk of AD *after* testing, with possible increased depression or distress regarding ApoE testing. Notable is the fact that participants who received the extended protocol prior to disclosure confirmed a significant decrease in AD concerns (Ashida et al., 2010). This data caused researchers to conclude that a pre-test and post-test assessment of perceived AD risk could provide important information and may benefit participants in the form of additional interventions to assist in aligning perceived versus actual risk. This alignment of perceived versus actual risk could be beneficial, considering the fact that 80% of all participants reported a higher perceived risk estimate than actual risk, with half overestimating by over 20% (Ashida et

al., 2010). Researchers may also want to consider whether or not high pre-test, perceived risk participants could benefit from genetic testing or whether this information should serve as a screening method for notifying researchers to provide interventions *prior* to ApoE testing. The assessment of perceived risk could provide researchers or clinicians with an opportunity to identify the individuals that could benefit most from interventions *before* genetic testing occurs (Ashida et al., 2010).

Given that the data found that participants who received the extended disclosure protocol with face-to-face education reported a significant decrease in AD concerns (Ashida et al., 2010), the researchers concluded that participants with less education *before* test result disclosure could be more negatively affected psychologically by ApoE test results. As AD research progresses, providing participants with the current scientific knowledge could prevent or reduce adverse psychological effects during genetic disclosures, but this would need to be independently evaluated. They also concluded that the positive ApoE ε4 individuals with increased AD concerns after genotype disclosure could benefit from additional support and interventions to help further minimize negative impacts. The importance of implementing supports and interventions was further emphasized in 2010 given that no effective known preventative or treatment strategies were available at that time for AD. The researchers determined that further research would be necessary to identify the specific supports and interventions to implement. Finally, this study revealed that communicating genetic test results to others could be a supportive tool that helped participants adapt psychologically to the changes realized during their genetic test results disclosure (Ashida et al., 2010).

In 2011, a poster presentation was done to analyze the effect of ApoE disclosures on exercise and mental activities (Klopfenstein et al., 2011). During this analysis, the researchers hypothesized that post disclosure, the ApoE-ε4 carriers would be more likely than non-carriers to report changes in exercise or mental activities. This analysis involved 451 participants with first-degree relatives who had AD and who had participated in the prior REVEAL trials. These participants received risk assessments based upon their background (e.g., family history, ethnicity, and gender) and ApoE genotype, resulting in a risk range of 13-74%. They were asked to either confirm or deny changes to their exercise plans or mental activities after genotype disclosures at both 6 weeks and 12 months. After adjusting for age, gender, race, education, and randomization, a logistical regression was conducted, which revealed an increase in exercise plans and mental activities for both carriers and non-carriers, with a 5-10% larger increase for ApoE-ε4 allele carriers versus non-carriers. Researchers concluded the knowledge of ApoE genotype motivated individuals to change exercise and mental activities. The researchers noted that these behaviors are not proven to prevent AD but are promoted as a possible method of reducing AD risk, which may explain the activity increase for positive ApoE-ε4 participants (Klopfenstein et al., 2011).

An additional study was performed in 2011 that focused on the perceptions of ApoE genetic testing disclosure for first-degree relatives of patients with AD (Christensen et al., 2011). During this study, conducted between 2003 and 2006 from data of the REVEAL II trial, 293 participants were asked to rate 11 benefits (pros) and 10 risks (cons), before genetic risk disclosure and again 12 months after (Christensen et al., 2011). The purpose of this study was to analyze participants' perceptions regarding the positive and negative aspects of genetic testing

and the predictors of test use. The researchers wanted to compare participant's initial expectations with the real experience.

Participants were randomized into two separate educational conditions: 1) the standard condition involving in-person educational sessions with a genetics counselor and a direct discussion with the genetics counselor, and 2) the condensed condition, which substituted a brochure for the genetic counselor's discussion and provided the participant with a chance to ask questions (Christensen et al., 2011). Participants completed a baseline assessment and received educational preparation; they also received a second informed consent with an in-person clinician discussion. The information participants received during this process included the itemized list of benefits, risks, and limits of AD genetic testing (Christensen et al., 2011). Written messages to both the participant groups provided information and printed materials on the itemized listing of the pros and cons of AD genetic risk testing.

Participants rated the pro items higher than the con items on the provided list at baseline and 12 months after AD test result disclosure (Christensen et al., 2011). At the 12-month time, ratings of some listed pros did decrease, while the listed cons remained the same. Participants were also assessed in the areas of prevention. Positive prevention outcomes increased over time when compared to baseline. with individuals increasing their implementation of positive health practices and their compliance to suggested medical treatments. ApoE-ε4 positive participants consumption of dietary supplements and vitamins (Christensen et al., 2011).

There were a few findings that surprised researchers. The first was a decline in participants' interest in arranging for long-term care insurance. Researchers felt that this behavior supported the belief that a lack of clear answer for participants regarding onset of AD,

deterred them from purchasing long-term care insurance (Christensen et al., 2011). This pattern appeared to support the belief that a lack of answers about AD onset was a stronger con variable during follow-up than at baseline (Christensen et al., 2011). The second area was a decline in participants' willingness to provide their children with their AD risk information, with ApoE carriers endorsing lower willingness than non-carriers during follow-up. Researchers surmised that this may have been the result of participants' guilt regarding passing AD on to their children, or participants' perception that receiving "bad" news is more stressful than receiving "good" news. Finally, the participants' desire to contribute to AD research subsequently declined at follow-up, for which researchers mentioned the possibility that the perceived burden of participating in research may have affected their motivation during follow-up (Christensen et al., 2011).

Researchers addressed the limitations of this study, acknowledging that their approach did not allow them to determine the reasons for changes in perceptions from pro to con (Christensen et al., 2011). They also confirmed that any of the research procedures could have contributed to participants' perception changes. Further, participants without data at 12 months were excluded from researchers' analysis. Also, the surveys contained closed-ended items that may not have captured all the pros and cons for each participant. Lastly, the potential for false-positive findings was increased because significance levels were not adjusted for the number of comparisons conducted. The authors stated this was due primarily to the fact that this study was not powered for the secondary analysis that was done (Christensen et al., 2011).

This study did reveal possible significant implications regarding the method used when delivering genetic services, as well as the influence participants' positive attitude had towards

AD genetic testing, including ApoE genetic testing (Christensen et al., 2011). Aligning expectations with true outcomes through discussions and education was also reinforced as a recommendation when moving forward with this type of research. Researchers also reinforced the importance of the right balance between effectiveness and practicality through pretest education and screening of participants to be sure they are making informed decisions about genetic testing (Christensen et al., 2011).

Furthering this educational need in genetic testing for AD, a 2012 study compared research to determine whether the length of patient's genetic testing education affected their level of knowledge and ability to recall the AD genetic risk factors (Roberts et al., 2012). The study was a randomized, controlled trial at four sites with a final analysis of 264 first degree relatives of individuals with Alzheimer's disease. Participants were excluded if they scored in the clinically significant range on measures reflecting declining cognitive functioning, depression or anxiety was present, or if they had more than one first degree relative with AD.

During their pre-disclosure education appointment, participants were placed in one of two groups, 1) those provided with in-person education sessions, (e.g., extended protocol or EP) and 2) those provided with a mailed brochure educating them (e.g., condensed protocol or CP; Roberts et al., 2012. The information provided included AD risk factors and the relationship between the ApoE risk factor and AD. Specifically, both groups received a formal definition of AD, general AD risk factors (e.g., family history, age), AD risk level within the general population, ApoE genotype risk of AD, ApoE testing procedures, a preview of ApoE risk assessment information, and ApoE testing benefits, risks, and limits. The extended protocol included a study clinician who explored any possible psychosocial issues regarding testing

participants. In contrast, the condensed protocol only addressed psychosocial issues with participants if they initiated the discussion. Unfortunately, the details of discussions regarding these psychosocial issues were not provided, as the researchers in this study were focused on genetic risk information knowledge and recall. The final activity for both participant groups involved a blood draw with samples sent to the lab for ApoE genotype testing (Roberts et al., 2012).

Subsequent in-person disclosures were scheduled with both groups, including ApoE testing results along with their estimated lifetime risk of developing AD from birth to 85 years old. Lifetime estimates were based upon gender and AD gene risk curves for Black and Caucasian participants. The lifetime risk provided to participants with one copy of the ApoE ε4 allele ranged from 25-74%; while participants without an ApoE ε4 allele fell within the 13-50% range. Participants were also provided with a graphic depiction of their AD risk when compared with the general population and their first-degree relatives with AD. Researchers used a script to explain their AD risk to participants. Participants' personal medical information and family history of AD helped the researchers generate each individual's risk estimate. A one-page summary regarding risk estimates with the limits was also provided to participants. Follow-up surveys were given to participants for completion at 6 weeks and again at 6 months after their ApoE risk disclosure (Roberts et al., 2012).

The measures utilized during this study included: a demographics self-report questionnaire; and an objective skills test, using an eight-item scale developed by Lipkus in 2001, assessing participants' understanding and knowledge of ApoE and AD risk (Roberts et al., 2012). The assessment of knowledge and risk included a combination of true/false and multiple-

choice questions. The area analyzed by researchers included the length of time participants spent face-to-face with clinicians, any change over time in participants perceived risk of AD, participants' risk knowledge regarding ApoE genotype and other risk factors, recall of lifetime risk estimates provided at time of disclosure, and their ApoE genotype, along with their allele type (0, 1, or 2; Roberts et al., 2012).

Researchers used descriptive statistics to characterize participants' outcomes and demographics during their data analysis (Roberts et al., 2012). The differences between participants' knowledge and recall during the EP and CP was analyzed using $\chi 2$ and *t*-test statistics. The researchers utilized repeated measures analyses of variance to determine the differences between the EP and CP groups and the effects of key demographic variables on these two groups (Roberts et al., 2012).

The results revealed that 42% of participants carried at least one of the ApoE ε4 allele (Roberts et al., 2012). The length of time with clinicians varied between the two groups. The CP participants had two in-person sessions that took approximately 34 minutes while the EP participants had three in-person sessions that took approximately 77 minutes. The researchers' analysis found no negative correlation between the amount of time spent with the research clinician and AD risk knowledge or AD risk recall. Both groups (EP and CP) achieved significant gains at 6 weeks when compared to baseline. However, at 6 months a significant proportion of participants within both groups could not retain details about their risk disclosure sessions, such as knowing which ApoE ε4 allele was known for an increase AD risk. Researchers mentioned how this research adds to growing literature supporting brief, alternative approaches to genetic counseling for adult-onset disorders such as AD, which is the type of work

that began in the context of the BRCA gene testing. They also mentioned the use of computer aided genetic counseling programs that have been used for breast cancer with satisfactory outcomes. Telephone counseling was also mentioned as having a place as a stand-in for in-person counseling regarding BRCA testing. However, researchers did qualify this by indicating that certain situations require in-person sessions and extended time, like genetic test results for Huntington disease (Roberts et al., 2012).

Genetic education and counseling regarding psychosocial adjustment and health behavior outcomes fell outside this study's scope of analysis (Roberts et al., 2012). Further, researchers emphasized the fact that their findings should not be generalized to personal genomic service companies with educational and counseling provided via telephone and website only. Additional research in diverse populations regarding brief genetic education protocol for complex disease was also suggested by researchers (Roberts et al., 2012). In addition, the decrease in participant retention at 6 months should be further analyzed in future research within this area to help to better understand why this decline happens and what may be done in the future to prevent such an occurrence.

In 2014, another study was done to analyze the effect that ApoE-ε4 disclosures had on healthy behaviors such as diet and exercise (e.g., positive and negative outcomes; Hietaranta-Luoma et al., 2014). This study included 122 participants (ages 22-67) without any long-term medications or chronic medical conditions. Participants were randomized into two groups, one control group (n = 61) and one intervention group (n = 61) The intervention group was subsequently divided into two subgroups with 40 placed in the low risk, ApoE-ε4 negative group and 21 placed in the high risk, ApoE-ε4 positive group. Overall, five participants dropped out of

the study before completion and four started long-term medications, excluding them from the study and leaving 113 participants. Further, four additional participants were excluded due to incomplete assessments and there were two outliers, resulting in 107 total participants for the study (Hietaranta-Luoma et al., 2014).

All participants were provided with health information based upon their ApoE genotype, using the Extended Parallel Process Model (EPPM) with communication pertaining to cardio-vascular disease (CVD) and ApoE genotype (Hietaranta-Luoma et al., 2014). The EPPM illustrates how individuals react to fear-inducing messages. The customized health message provided to participants varied, with the message to ApoE-ε4 positive participants emphasizing the importance of a change in diet and increased exercise. The ApoE-ε4 negative participants' message emphasized the interactions regarding food and activity within their lifestyle. The control group received general information regarding the study and general health information on lifestyle and CVD risk based upon health and nutrition recommendations and studies. The health information obtained included four parts: response efficacy, self-efficacy, susceptibility and severity. These communication sessions occurred at baseline, 10 weeks, 6 months, and 12 months, with the last communication being a follow-up meeting (Hietaranta-Luoma et al., 2014).

The assessments included questionnaires regarding diet, alcohol use, physical activity, and included the Health and Taste Attitude Scales (HTAS), which involved measurements of psychology and behavior (Hietaranta-Luoma et al., 2014). The questionnaires used to measure these behavioral and psychological changes in participants included the following: 1) Dietary fat quality (Finnish Heart Association, 2014), 2) Consumption of vegetables, fruits, and berries (Finland & FIN-DD, 2008 & 2009), 3) Consumption of foods containing excessive fat and sugar

(Helsinki, National Institute for Health and Welfare, 2008), 4) Alcohol consumption (Helsinki, National Institute for Health and Welfare, 2008), 5) Leisure time physical activity (Helsinki, National Institute for Health and Welfare, 2008), and the Health and Taste Attitudes Scale (HTAS; Roininen et al., 2001). These assessments were given during baseline and at follow-ups covering psychological, behavioral, and clinical factors (Hietaranta-Luoma et al., 2014).

The interventions implemented included six different communication sessions with the first being a lecture presentation regarding healthy diet and lifestyle with a nutritionist (Hietaranta-Luoma et al., 2014). Sessions two and five provided information on participant's ApoE genotype and health messages through the mail, which was based on the EPPM for communication of ApoE genotype for AD. Session three was an optional lecture on ApoE, including gene and diet interactions, from a professor specializing in nutrigenomics and nutrigenetics. The fourth and sixth communication sessions implemented the ethical principles of human experimentation as set forth in Declaration of Helsinki guidelines, with personal participant-doctor discussions that were completely voluntary (Hietaranta-Luoma et al., 2014).

The researchers analyzed the connections between ApoE genotype, method of intervention session, and the health behavior changes (e.g., diet and exercise; Hietaranta-Luoma et al., 2014). This analysis was done using an analysis of variance among the means of these different variables. Physical activity and alcohol use was analyzed using a X^2 test (Hietaranta-Luoma et al., 2014).

The conclusions reached by researchers for this study were that personal health information regarding genetic screeners may have positive effects on health behaviors. They also concluded that these study results recommend focusing on only a few health behaviors at a

time based on genotype-based health information (Hietaranta-Luoma et al., 2014). The researchers also concluded that repetition has a significant role in health information and its promotion of a healthy lifestyle. The exploratory nature of this study calls for further research in this area (Hietaranta-Luoma et al., 2014).

The early 2000's saw the emergence of direct to-consumer (DTC) genetic testing. In this context, disclosure is a means of providing consumers with access to their genetic information without physician involvement. Early on, this approach brought much debate and controversy. Ultimately, this new trend prompted a 2014 longitudinal, web-based customer survey regarding level of customer interest in receiving AD risk information (Roberts et al., 2014). The study lasted from March 2012 through April 2013 and included data from 1,004 customers who had a mean age of 50 years old. Survey assessments were done at baseline prior to disclosure and followed-up with surveys at both 1 week and 6 months after ApoE genotype disclosures. The researchers did not specify which measures were used to determine levels of anxiety, depression, or distress. However, a comparison of the two groups (Apoe-ε4 negative and Apoe-ε4 positive), revealed no post-disclosure difference at either 1 week or 6 months in participants' depression or anxiety, but their distress was slightly elevated for both groups. The two groups also showed an increase in perceived risk of AD at 1 week and 6 months. Test-specific distress (e.g., specific distress pertaining to the genetic testing process, not test results per se) was found to be slightly elevated for the Apoe-ε4 positive group. The Apoe-ε4 positive group was also found to be more likely to make pro-health (e.g., vitamins/supplements) and life planning insurance changes. There were no significant post-disclosure group changes to diet and exercises (Roberts et al., 2014).

These researchers concluded from the test findings that AD genetic risk information had a strong appeal for consumers and that AD risk disclosure generated more preventative health behaviors and advance planning. They also noted that the study found participants receiving higher risk results demonstrated slight elevations in distress but no clinically significant symptoms of anxiety and depression. (Roberts et al., 2014).

Another study in 2016 analyzed the psychological, behavioral, and social effects of disclosing genetic and nongenetic AD biomarkers to healthy research participants (Bemelmans et al., 2016). These researchers performed a literature review, including a search of eight scientific databases (e.g., Embase, Medline, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials, Web of Science, PubMed, and Google Scholar), with three independent reviewers screening records to identify relevant articles and remove duplicates. The method used by reviewers was a systematic review in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement (Bemelmans et al., 2016).

These reviewers used varied search terms in locating relevant articles including: dementia, biological markers, genetic testing, disease risk, disclosure, and psychological behavioral and social factors (Bemelmans et al., 2016). The inclusion criteria for the articles within this meta-analysis were only articles that met the following criteria: articles reporting on empirical evidence, published in peer-review journals, were reporting on actual/hypothetical disclosure, and written in English. The behavioral effects that were reported on were only those attributed to risk disclosure. The social effects reported were within an individual's social context rather than a broader social context. The psychological effects reported were limited to

emotions, mood, and cognition. Any studies involving participants with a prior diagnosis of dementia or MCI were excluded from this meta-analysis. If several articles had the same or similar outcomes, reviewers selected the most relevant article or most extensive report for their analysis. The extracted results were separated and presented by effect group with outcomes in both quantitative and qualitative formats (Bemelmans et al., 2016).

There were 14 studies that met the inclusion-exclusion criteria with 12 studies being quantitative and 2 studies being qualitative (Bemelmans et al., 2016). The 12 quantitative studies varied in their number of participants from an $N = 76$ to an $N = 4036$. The 2 qualitative studies had an $N = 60$ and $N = 79$. The majority of these studies involved follow-up assessments at 6 weeks, 6 months, and 12 months. Out of the 14 studies reviewed, 11 of them reported from data that was obtained through randomized control trials during the REVEAL studies (e.g., REVEAL I, II, and II). The additional studies were not randomized but involved cohort, case-control, and survey designs. Out of the 14 articles reviewed, four reported on social effects and six each reported on behavioral and psychological effects. The effects of disclosure were extracted from the results sections of eligible studies and these effects were then grouped by outcome measure of psychological, behavioral, or social (Bemelmans et al., 2016).

The assessments included in these studies were as follows: BAI (Beck, 1988), CES-D (Radloff, 1977), IES (Horowitz et al., 1979), WMS-R (Elwood, 1991), ROCFT (Rey, 1941; Osterrieth, 1944), MIA questionnaire (Dixon et al., 1988), Memory Functioning Questionnaire (Gilewski et al., 1990), a self-developed questionnaire (Romero et al., 2005), and a clinical interview.

This meta-analysis revealed that the psychological, behavioral, and social effects of ApoE disclosure whether positive or negative did not result in increased anxiety or depression (Bemelmans et al., 2016). However, disclosure of ApoE positive test results were found to cause an increase in genome testing distress (e.g., distress due to the genetic testing process not test results per se), health-related behavior changes, and long-term care insurance uptake, and could influence memory functioning. In contrast, the participants who were disclosed ApoE negative test results displayed no increase in the above-mentioned areas.

Those participants who had a family history of AD did not demonstrate altered beliefs pertaining to the cause of AD or their personal risk of AD (Bemelmans et al., 2016). In fact, reviewers noted that these ApoE disclosure studies frequently resulted in relief when received by low-risk participants (ApoE negative genotypes) and resulted in a perceived "safe" disclosure for participants receiving high-risk test results (ApoE positive genotype). The majority of the participants in these studies had former direct relatives with AD but were healthy themselves and hence considered "safe" by the researchers working with them. Reviewers did clarify that because the meta-analysis involved participants with a family history of AD, this blunted impact or effect would be expected due to their prior knowledge of AD family risk. The AD family history of participant groups within this literature review made generalization of this research to other population groups impossible. Reviewers noted that research participants without any AD family history may be more substantially impacted by an ApoE genotype disclosure (Bemelmans et al., 2016).

As for the overall lack of depression results in this meta-analysis, more detailed interpretation was suggested by reviewers (Bemelmans et al., 2016). In one study, reviewers did

find that 9% of participants scored above the clinical cutoff scores for depression after 12 months despite being below this threshold at baseline. Another study revealed that 15-30% of participants did agree to a statement of feeling depressed after their high-risk AD disclosure, while none of the low-risk participants endorsed feeling this way. Reviewers also noted that all these studies involved participants who passed psychological screeners rather than individuals with some psychological problems at baseline, which could affect the impact of disclosure on participants (Bemelmans et al., 2016).

Reviewers also mentioned the negative effect ApoE genotype disclosures could have on the perception of cognitively impaired participants, specifically, memory functioning (Bemelmans et al., 2016). They suggest that labelling someone as high-risk regarding AD may create a negative expectation, similar to drug trial negative placebo effect. In high-risk AD participants, reviewers note that these negative expectations could result in a real level of diminished memory function (Bemelmans et al., 2016).

When analyzing behavioral changes, reviewers discovered that high-risk participants engaged in many positive behaviors such as an increase in long term care insurance, future planning, and arranging personal affairs (Bemelmans et al., 2016). They also discovered some negative behaviors such as increased dietary supplement intake that may have negative consequences, including providing a false sense of control over the situation (e.g., vitamin E; Bemelmans et al., 2016). One of the qualitative studies reviewed during this meta-analysis was done in 2006 and involved exploring the impact of ApoE genetic risk disclosures on research participants. The participants involved in this study were adult children of individuals in the REVEAL study (Gooding et al., 2006). The participants ($N = 60$) were randomized and received

risk counseling according to family history and ApoE genetic test results with two groups, an intervention group and a control group. The qualitative research team for this study included a variety of professionals, such as psychologists, genetic counselors, doctors, nurses, and anthropologists. This team created an interview guide for this study exploring the participants' experiences with AD and their ApoE genetic testing. No participants were excluded from this study. The interviews were conducted in person with participants from December 2002 through January 2004. The interview questions were open-ended inquiring about participants experiences with AD , with topics regarding perception of developing AD, perceived cause of AD, perceived control of AD, motivation to participate in past study, and reactions to testing results (Gooding et al., 2006).

After the interviews, 20 randomly selected interview transcripts were repetitively coded for themes until researchers reached an interrater reliability of 76% (Gooding et al., 2006). The 40 additional interview transcripts were then coded and data reports were created for analysis. The researchers' data analysis included datasets pertaining to disease susceptibility, perceived threat, dispositional coping/control styles, coping effect and emotional adaptation. Out of the 60 participants, 17 discovered they had the positive ApoE ε4 allele, 24 discovered they had the negative ApoE risk result, 15 received only a family history risk assessment (e.g., control group) and 4 declined to complete the study (Gooding et al., 2006).

The researchers found that 46 participants (77%) reported feeling an increased risk for AD due to their family history, with some (n = 10) revealing they felt this when their parent was diagnosed with or weakened by AD (Gooding et al., 2006). Several participants who had multiple family members with AD felt they were at an extremely high risk for the disease

because of this history (*n* = 12) and one individual believed she was at less of a risk because only her mother had AD. Other participants felt they were at risk of AD because they shared some traits of the affected AD parent (*n* = 7), and others (*n* = 2) distanced themselves from the AD parent by noting how different they were from that parent. Ten of the participants connected their family history concerns with a desire to know their ApoE risk status.

In addition, 29 participants (48%; 13 negative, 9 positive, and 7 control group/declined group) were frightened or worried about developing AD, and reported feeling threatened by their AD risk (Gooding et al., 2006). There were 17 participants that related their fear of being a burden to their desire for genetic testing and concerns about AD. This correlation was stronger if participants struggled to care for their AD parents or were still considering having children themselves. Participants also feared having their careers ended early or being unable to enjoy retirement (*n* = 6). There were 14/19 participants (78%) who reported their primary reason for participation was their worry about their own AD risk. Fear of developing AD motivated 9 participants to learn their ApoE risk results, and other participants reported that this same fear was their reason for not learning this genetic information (Gooding et al., 2006).

Half of the participants (*n* = 35; 58%) indicated their general preference was to seek out genetic testing information, with 11 participants feeling it was necessary to collect information about a person's health to make informed decisions (Gooding et al., 2006). Four participants mentioned knowledge being power as to their preference for this information. Ten participants reported that needing to feel control over situations was their reason. In this regard 33% (*n* = 20) indicated they were a person who needs to feel control or take charge of their health. Most participants (*n* = 45) believed the act of obtaining genetic test results was confronting their AD

risk and asserting control. Two other individuals reported they coped by avoiding and felt obtaining their genetic information was too much of a threat for them, so they declined participation (Gooding et al., 2006).

Regarding emotional reactions to ApoE results, twenty-four (40%) participants (10 negative, 10 positive, and 4 control/declined) confirmed having adequate emotional resources or coping skills to handle test results (Gooding et al., 2006). Another thirteen (22%) of participants (10 negative, 2 positive, and 6 control/declines) reported worrying about their emotional response to genetic results, with two of these participants refusing to continue with testing. Half (n = 30) of participants confirmed encountering friends or family who told them they would never consider genetic testing for AD, with fifteen participants reporting the feeling that an individual's ability to deal with their genetic risk information was impacted by personality and coping skills. There were 47% of participants (n = 28) who viewed ApoE genetic testing as a method to plan for the future with most of those (n = 17) mentioning "getting things in order" (Gooding et al., 2006, p. 264). There were three participants who planned to use the information to determine whether to get long term care insurance. Five participants hoped that the information would prepare them and their families for the possibility of developing AD. Seven participants expressed their desire for testing as a way to relieve their children's care burden. Nearly half the participants (n = 29; 48%) reported feelings of relief post-disclosure, including four who were positive for the ApoE ε4 allele. These same ApoE positive participants also expressed relief that their risk was not as high as originally perceived because they were now able to reframe risk based upon the additional education received during the study. However, six positive ApoE ε4 allele carriers (35%) did express greater concern about AD risk. They

described their test results as, “depressing, frightening, and disappointing” (Gooding et al., 2006, p. 265). The rest of participants (n = 21) expressed neutral thoughts without any worry or relief, which included seven participants that were ApoE ε4 allele positive carriers. These positive carriers connected their lack of emotion to the inability of ApoE to predict AD and their prior acceptance of AD risk (Gooding et al., 2006). The researchers in this qualitative study concluded that ApoE genetic risk testing could be a useful coping method for some individuals at risk for AD, with it possibly assisting in emotion-focused strategies (Gooding et al., 2006).

These researchers mentioned their findings included limited demographics not representative of the general public and therefore not generalizable. They added that participants’ biased interests in genetic testing and willingness to participate impacted the sample, noting that four participants interviewed declined further analysis and reported factors of threat, uncertainty, and control. Finally, researchers pointed out that the interviews done were performed months after genetic testing disclosure and therefore were influenced by the passing of time (Gooding et al., 2006).

The second qualitative study analyzed during this 2016 meta-analysis pulls from empirical findings within interview studies in both the U.S. and Canada with a focus on the idea that expanding genetic testing practices will likely fundamentally alter family relationships (Chilibeck et al., 2011). These researchers believed that it was more likely the pre-existing family dynamics and perceptions of family susceptibilities for disease would be the catalyst in interpreting genetic testing results and not the testing results themselves. They selected the ApoE allele for their analysis because of it being a susceptibility gene (e.g., a gene only contributing to disease; Chilibeck et al., 2011).

The findings within this qualitative study were obtained from participants of the on-going NIH approved REVEAL study from 2005 (Chilibeck et al., 2011). These participants have one or more relatives diagnosed with AD and were recruited from AD research registries or were self-referrals. After completing the 2005 REVEAL study, seventy-nine participants agreed to participate in open-ended interviews from 2004-2006 given by a small group of anthropologists. The age range of this sample was from 37 to 76 years old, averaging 16.8 years of education with 86% of the sample population being female (Chilibeck et al., 2011).

The findings of these anthropology researchers indicated that only 27% of participants recalled ApoE test results a year after participation, with 23% unable to recall their genotype or risk estimate at all. Participants stated things such as, "I have a lower risk than imagined," or "I have the bad gene," or "I'm next to worse" (Chilibeck et al., 2011, p. 1770). They also stated things like, "I'm an ε4-ε4 allele whatever that means" (Chilibeck et al., 2011, p. 1770). Researchers found that participants instead articulated their personal risk using family expressions of family histories or resemblances, mentioning things like "running in the family" or "part of the family history" or "in the family line" rather than their ApoE genetic test results (Chilibeck et al., 2011, p. 1770). These researchers also mentioned one participant who fused the two ideas of genetics with family risk (e.g., superimposition) to gain clarity when she stated "They'll have a high family risk, but other than that, who knows…I don't know what their genetics are but I do think about what their chances are…My sister had a small stroke many years ago and she's at risk, I mean, she has the same family history that I have [ε3/ε4]" (Chilibeck et al., 2011, p. 1770). The researchers surmised that by blending the abstract with the concrete, these superimpositions with genetic information make it easier for individuals to

emphasize that the genetics is not new information but only confirmation of family information they already knew. This blending is especially easy to do when genetics and family history information is similarly aligned. Researchers also mentioned that superimpositions are harder to engage in when genetic risks and familial information conflicts, citing another participant as saying, "I found out my results. My risk was just minimally more than others…To me, that makes no sense, I really believe I don't have much of a chance of missing it just by genealogy…my mother's family is all – there's nothing else, just Alzheimer's. So technically, I should feel better. But I don't believe it" (Chilibeck et al., 2011, p. 1770). Other participants were found to search their family history for evidence supporting their elevated risk stating, "This information [that I am at increased risk] affects my entire family, my children especially; because I carry a gene it is quite possible that they have this also. But the only case [of AD] I have really known was my Dad...I look at his twin sister now and I'm saying how did he get Alzheimer's…she doesn't have Alzheimer's?" (Chilibeck et al., 2011, pp. 1770-1771). Only 4% of participants listed genes as the only explanation regarding AD. Researchers also noted that AD genetic explanations are framed by mentioning several factors such as genetic susceptibility, predisposition, or vulnerability to AD, which are then aggravated, mitigated or prevented by other factors within the individual or their environment. For example, one participant stated, "You have the genetic potential: no question. Whether it shows up or not has a lot to do with what you do and your environment [ε3/ε4]" (Chilibeck et al., 2011, p. 1771).

Their findings regarding how individuals and their families pursue, interpret, and utilize genetic test results was also found to be dependent upon the nature of the disease in addition to perceived family traits and dynamics (Chilibeck et al., 2011). Researchers noted that because

AD typically has a later onset and gradual progression, the fear of AD is secondary for most individuals versus cancer or heart disease. They also mentioned the worries of being afflicted with AD are also usually secondary to their immediate concerns regarding caregiving for family, which these researchers refer to as "kinning" (Chilibeck et al, 2011, p. 1772). Participants were found to be less concerned with their personal AD risk and more concerned with what they may pass on to family or the social and financial difficulties their family may inherit because of their AD. For example, one control group participant indicated, "It's so heartbreaking to see families that lose everything [to pay for care] …cause then you don't have anything to pass on to your children" (Chilibeck, et al., 2011, p. 1772). The researchers concluded these findings demonstrated participants' familiarity with fragmented facts and partial information, surmising that they are approaching genetic susceptibility similar to other life uncertainties (Chilibeck et al., 2011).

These researchers also analyzed interviews done with first-degree relatives of late-onset AD patients in Canada from 2002 and 2003 (Chilibeck et al., 2011). The 40 participants ranged from 29 to 70 years old with 58% being female. These participants were different from the prior REVEAL participants in that they had not been exposed to any information about the genetics of AD. The researchers in this analysis found that no participant introduced the ApoE gene during the interview, but approximately 50% of them believed AD has something to do with genetics. The majority of these participants also interchanged genetics and heredity when discussing the cause of AD, with one individual stating, "I tell myself that the genetic are responsible for the disease, I think it's family baggage…It's true that there were hereditary antecedents. My grandmother suffered through Alzheimer's and my aunt also did" (Chilibeck et al., 2011, p.

1772). These participants also demonstrated a connection between similar family traits and AD risk, with one individual indicating she believed her brother would be more likely to get AD than she would because of his shared features with their mom with AD. These participants also emphasized family history and personal experiences with confronting AD, and some questioned the relevance of AD genetic testing with one participant stating, "I don't see the point of knowing. I also believe people with AD know there is something wrong…My mother knew…she said to me, 'I'm not what I used to be" (Chilibeck et al., 2011, p. 1773).

The researchers during these two analyses concluded that participants beliefs on AD causation and personal risk are similar, even though their exposure to genetic information on AD was different (Chilibeck et al., 2011). They also concluded that this research supports the belief that genetic technology will not illicit profound changes in kinship or conceptualized family/personal risks for AD. Researchers posited that these findings also support heredity and kindship as significant tools in assessing and interpreting genetic information (Chilibeck et al. 2011).

Another study done in 2016 sought to answer the question of whether preclinical research participants would want to know their ApoE genotype and the amyloid positron emission tomography (e.g., amyloid PET) status and if so, why would they want this knowledge (Ott et al., 2016). Since 2011, research surrounding these prodromal participants has been of great interest to the National Institute on Aging and the Alzheimer's Association, due recent clinical trials for AD modifying drugs believed to most benefit individuals during their preclinical stage of AD. Several years prior to this 2016 study, the unknown response by prodromal participants to their AD risk factor was debated ethically and in relation to positive and negative outcomes (Arribas-

Ayllon, 2011; Shulman et al., 2013; Lawrence et al., 2014). The two biomarkers involved in this study were the ApoE genotype and amyloid PET status, as they are both considered reliable in determining AD risk in the future (Ott et al., 2016).

Participants for this study were identified using registries created by web-based AD prevention outreach organizations throughout the country, and the participants for this specific study were selected from the Rhode Island Alzheimer Prevention Registry (RIPR; Ott et al., 2016). Research participants were invited to voluntarily attend an office visit where they would sign a consent after being interviewed over the phone regarding demographic and background information, along with family history and other medical and psychiatric history. Participants with an AD diagnosis, a dementia disorder, a major psychiatric condition, Down's syndrome, or other cognitive/learning disability were excluded from the study. Further, participants determined to be MCI by the Minnesota Cognitive Acuity Screen (MCAS) were included in the study, 16.4% of current registered participants (Ott et al., 2016).

An anonymous 25 item online questionnaire was provided to 207 people who had been a part of the RIPR since 2014 (Ott et al., 2016). Participants received no additional educational materials prior to completion of this survey. During this survey, participants were asked if they wanted to receive their ApoE genetic status and amyloid PET status, and if so, what was their reason for wanting this knowledge. The additional survey questions pertained to demographics and the participant's knowledge regarding ApoE status in a true/false format "APOE: 1) Is a genetic risk factor for Alzheimer's disease. If you have this risk factor, will you definitely get Alzheimer's disease if you live long enough; 2) Is a genetic risk factor. If you have this risk factor, you are more likely to get Alzheimer's disease than those who do not; 3) Has not yet been

established to be a risk factor for developing Alzheimer's disease; 4) Is commercially available; and 5) Is routinely done as part of the diagnostic evaluation for Alzheimer's disease performed by most physicians" (Ott et al., 2016, p. 24). The knowledge questions pertaining to amyloid PET were also true and false ApoE statements "APOE: 1) is a brain damage imaging test that is used to diagnose dementia; 2) Is a brain imaging test that can be used to help rule out or exclude Alzheimer's disease as the cause of dementia; 3) Is a brain damage imaging test that can be used to help rule out or exclude Alzheimer's disease as the cause of dementia; 4) If showing no amyloid in the brain, means you will not develop Alzheimer's dementia; 5) Is commercially available; and 6) Is routinely done as part of the diagnostic evaluation for Alzheimer's disease performed by most physicians" (Ott et al., 2016, p. 24). Researchers developed these questions after reviewing PubMed during the last 10 years regarding medical literature pertaining to ApoE and amyloid PET. This survey was completed by 164 participants with 138 completed via mail and 26 completed online (Ott et al., 2016).

The researchers on this study discovered that out of the 23 participants who already knew their ApoE or amyloid PET status, none reported feelings of hopelessness, depression or suicidality upon receipt of this information (Ott et al., 2016). The other participants (80.3%) were unaware of their ApoE but reported a desire to know this information. The most common reasons for wanting to know their ApoE status was "to participate in AD research (75.9%), arrange personal affairs (74.1%), and move plans closer in the future (65.5%)." (Ott et al., 2016, p. 25). Further, 12.7% of the participants interested in knowing their ApoE status indicated they would use it to make plans for ending their life once their memory was gone (Ott et al., 2016). The most common reason participants gave for not wanting to know their ApoE status was their

worries about becoming anxious or depressed if they were ApoE positive. In addition, participants unaware of their amyloid PET status (80.6%) still wanted to know this information. This interest in amyloid PET status involved their perceived AD risk, developing AD, or having a related person with AD. Common reasons for these interests were "to participate in AD research (73.2%) and prepare spouse or children for their illness (60.2%)." (Ott et al., 2016, p. 26). Further, 11.5% of participants desiring their amyloid PET status confirmed they would use such status to make plans for ending their life once their memory was gone (Ott et al., 2016). The most common reason participants did not want their amyloid PET status was concerns about feeling depressed if they were positive. All of the participants surveyed were able to correctly answer 7 of the 10 knowledge questions regarding ApoE and amyloid PET status (Ott et al., 2016).

These researchers also reviewed supplemental research findings for surveys done prior to this study. D They discovered a study that utilized a more general survey of 314 individuals, and 79% of these participants reported they would take a hypothetical genetic test if it could predict their eventual development of AD (Neumann et al., 2001; Ott et al., 2016). In another survey that had been added to the Health and Retirement Study, it was discovered that 60% of 1,641 older adults were interested in genetic testing to help them learn about their risk of AD (Roberts et al., 2014; Ott et al., 2016). Another cross-sectional telephone survey with 2,678 adults in both U.S. and Europe discovered that 67% of these same adults reported being "somewhat" or "very likely" to take a medical test to detect early AD (Ott et al., 2016, p. 26). Other surveys reviewed by the current researchers revealed similar findings as the 2016 survey, with 4,036 participants in Arizona discovering a 70.4% interest in ApoE status for positive uses of healthier lifestyle

(90.5%), and obtaining long-term insurance (76.3%; Caselli et al., 2014; Ott et al., 2016). Similarly, 80.2% of Arizona survey participants were interested in their amyloid PET status. This 2016 research study expanded on the Arizona survey realizing that desire to know AD risk status extended beyond young individuals and individuals who were highly educated as was seen in the Arizona sample (Ott et al., 2016). The 2016 researchers concluded a need for greater public education on AD genetic biomarkers, along with psychological screening tests for depression and opportunities for counseling (Ott et al., 2016). In fact, during a secondary prevention trial to this 2016 study, the researchers implemented a screening and disclosure process for amyloid PET status that included over 300 phone survey participants for a longitudinal assessment of disclosure impact (Ott et al., 2016). These researchers also noted that the ethics of disclosing AD genetic risk information is still being heavily debated (Ott et al., 2016). As for the psychological impact on individuals being disclosed their amyloid PET status, these 2016 researchers noted preliminary findings from the University of Kansas in which 25 participants had no increase in anxiety or depression during baseline or 6 months post-disclosure (Johnson et al., 2015; Ott et al., 2016). These Kansas participants also reported an increased intent to change daily diet and exercise habits, which was also reported for a subgroup of the 2016 registry (Johnson et al., 2015; Lim, et al., 2015; Ott et al., 2016).

Overall, conclusions of this 2016 study and the authors' review of supplemental research suggest that the majority of those interested in AD prevention want to know their genetic biomarkers for developing AD so they can use the information for life planning (Ott et al., 2016). Study limits mentioned by 2016 researchers pertained to a lack of generalizability to a broader demographic due to a participation group of older adults interested in AD prevention, the lack of

minority participants, and the presence of highly educated participants (Ott et al., 2016). These researchers suggested more diverse future research, as well as longitudinal studies, and studies addressing ethical issues (Ott et al., 2016).

In April 2017, the Food and Drug Administration (FDA) reported it would allow the DTC company 23andMe to sell genetic tests for disease risk directly to consumers, including genetic risk disclosure for AD (Kolata, 2017). Only two years prior, the FDA denied this same company the right to sell these tests directly to consumers. The FDA required that they could provide proof of the accuracy of their tests and confirm that customers understood the test results. By 2017, 23andMe had complied with the FDA's request. The FDA recently confirmed plans of an additional exemption, allowing other DTC businesses to market similar tests to consumers under the same requirements. The debate surrounding this decision was two-fold. Some people supported the FDA, arguing that individuals do not always need professionals and genetic counselor interventions to understand certain risks of disease. In contrast, there were others who believed this exemption sets a dangerous precedent. One of these individuals was Dr. Beck of the Parkinson's Foundation who believes that post-disclosure provides no way to go back in time and provide counseling if it has not been provided previously. Opposing this thinking was Dr. Green at Harvard who expressed his belief that those who inquire about AD risk testing are able to handle this information independently. Dr. Green also indicated that there is potential for some distress to occur, but stated this potential is not as much as people had anticipated. Specifically, regarding the ApoE4 genes, Dr. Green explained that even individuals with two copies of ApoE4 are not guaranteed to be diagnosed with AD (Kolata, 2017).

The change in procedure for DTC companies now involved these types of company being authorized to tell those tested about their personal risk (Kolata, 2017). Dr. Parvik at the University of Washington voiced that her concerns remain in the execution of disclosing results, adding she has seen patients who couldn't understand test results from DTC genetic testing. She expressed her hope that the delivery method used by DTC companies will not cause unnecessary medical visits. Dr. Pavik confirmed that the disclosure approach used when providing this genetic information is complex and can be challenging at times. (Kolata, 2017).

In 2018, researchers continued to explore the impact of other disclosure methods for ApoE risk factors, which included telephone disclosures (Christensen et al., 2018). This study randomized 257 participants from multiple sites (N = 257). The goal of this research was to provide more access and timely ApoE risk disclosures to individuals living in more rural areas. Exclusionary criteria included a history of hereditary AD (i.e., more than two relatives with AD onset under 60 years old), scores below an education-adjusted 87 on the Mini-Mental State Exam (MMSE; Folstein et al., 1975), or participants with severe anxiety or depression. Anxiety was screened using the Beck Anxiety Index (BAI; Beck, 1988), with severe anxiety being any score >25 on the BAI. Depression was screened using the 20-item Center for Epidemiological Studies – Depression Scale (CES-D; Radloff, 1977), with severe depression being any score >26 on the CES-D (Christensen et al., 2018).

Participants were part of a 2 x 2 factorial design with participants receiving the AD risk assessment either in person or over the telephone and either learning or not learning about ApoE's increased risk of coronary artery disease (CAD) at the same time (Christensen et al., 2018). Thus, equally randomized groups included: 1) AD only in-person disclosure, 2) AD only

telephone disclosure, 3) AD and CAD in-person disclosure, and 4) AD and CAD telephone disclosure. Participants were provided with a written summary of their risk assessments after their disclosure sessions (Christensen et al., 2018).

Results were assessed with questionnaires administered at 6 weeks, 6 months, and 12 months (Christensen et al., 2018). Additionally, after risk disclosures, verbal reminders of risk estimates and ApoE-CAD associations were provided to participants at 6 weeks and 6 months. As a safety and risk assessment measure, participants' anxiety and depression was monitored at each follow-up appointment; and if it increased by 15 points, participants were immediately interviewed by a genetic counselor (Christensen et al., 2018).

The assessments used during this study included Beck Anxiety Inventory (BAI; Beck, 1988), Center for Epidemiological Studies-Depression Scale (CES-D; Radloff, 1977), Impact of Event Scale (IES; Horowitz et al., 1979), and the Impact of Genetic Testing for Alzheimer's disease instrument (IGT-AD distress, Chung et al., 2009; Christensen et al., 2018). Higher IGT-AD (Chung et al., 2009) scores indicated more negative feelings and lower scores indicated more positive feelings (Christensen et al., 2018).

The results revealed that telephone disclosures occurred 7.4 days sooner than in-person disclosures (27.8 vs. 35.2 after blood draw, $p = 0.0002$; Christensen et al., 2018). Further, the telephone disclosures were 30% shorter in length when compared to in-person disclosures (e.g., 5-50 minutes in-person vs. 6.6 minutes on the telephone; $p = 0.001$; Christensn et al., 2018). Disclosure notes revealed that participants were more likely to discuss preventative measures in-person than over the telephone (26% vs. 14%, $p = 0.15$).

Throughout the study (i.e., at baseline, 6 weeks, 6 months, and 12 months) both

disclosure methods revealed that participants' anxiety and depression scores remained well below clinical concern cutoffs (Christensen et al., 2018). There was some suggestion that the telephone disclosures outperformed in-person disclosure on components of recall results. Specifically, telephone disclosure participants more accurately recalled their lifetime AD risk at 6 months (4.6% to 30.6%) and 12 months (2.1% to 29.6%) than in-person disclosure participants. At 12 months, ApoE positive participants were more likely than ApoE negative participants to recall their genotype (74.0% vs. 56.3%; $p = 0.008$). The participants who could not recall their AD risk estimates provided lower estimates. For instance, 64.2% of participants who had inaccurate lifetime risk recall and 61.5% of participants who had inaccurate remaining risk recall tended to underestimate their actual risk levels (Christensen et al., 2018).

The researchers in this study concluded that telephone disclosures of ApoE risk are safe and help meet service demands, even when results indicate a higher risk of AD (Christensen et al., 2018). They added that this research is encouraging considering the need for more efficient and effective approaches in conveying genetic risk information for complex diseases such as AD.

Also in 2018, an observational follow-up study was done in Finland to assess the long-term clinical and behavioral effects of receiving genetic risk information (Hietaranta-Luoma et al., 2018). Individuals were provided with their ApoE genotype that is known to contribute to both heart disease and Alzheimer's disease. This study continues the work done during a previous study in 2010-2011 monitoring the effect of disclosing the carrier status of the ApoE genotype (Hietaranta-Luoma et al., 2014; Hietaranta-Luoma et al., 2015a; and Hietaranta-Luoma et al., 2015b). This study monitored the disclosure effects of the ApoE-ε4 allele during a 5½

year follow-up that included clinical measurements and questionnaires regarding psychological and behavioral factors used in the 2010-2011 study (Hietaranta-Luoma et al., 2018).

Participants included those adults ages 26-73 years old who had participated in the prior intervention study and received their ApoE genotype (N = 70; Hietaranta-Luoma et al., 2018). Similar to the prior study, the same analysis was done on participants placed in the intervention group (e.g., received ApoE results in the beginning) and the control group (e.g., received ApoE results at the end). The 2018 data was compared with the data from 2010-2011 to identify any long-term behavioral and clinical effects.

These researchers confirmed that receipt of personal ApoE genetic risk status for CVD did provide motivation to improve health behaviors (Hietaranta-Luoma et al., 2018). For example, participants' largest improvements were seen in their plasma lipid values, triglycerides, and LDL cholesterol numbers when comparing high-risk groups to low-risk groups. The changes in this area were found to be due to the consumption of increased vegetables, fruits, and berries, and reduced consumption of sugars and fatty foods. Researchers also discovered that from 2011 to 2017 participants from the E4 and T3 group (e.g., groups receiving ApoE results at the end of the intervention) displayed improvement in nearly every category analyzed. These results prompted researchers to conclude that ApoE disclosure contributed to improved health behaviors. They concluded that participants' receipt of ApoE genetic risk status provided motivation to improve health behaviors, which resulted in measurable health improvements (Hietaranta-Luoma et al., 2018)

In 2019, an effort was made to provide some framework for larger scale disclosure of ApoE genotype test results, with a goal to use the information gathered as a model for clinician

disclosure of AD biomarker results to preclinical individuals (Langlois et al., 2019). A multidisciplinary committee was created entitled the "Genetic Testing, Counseling, and Disclosure Committee" (GTCD) with a goal to initiate the Alzheimer's Prevention Initiative (API) Genetic Counseling and Disclosure Process to be implemented during API Generation Program research trials (Langlois et al., 2019, p. 706). The purpose of this committee was to create a model of how to provide more consistent information throughout the ApoE counseling and disclosure sessions by utilizing standardized materials. This committee noted that although past traditional and condensed ApoE models of disclosure and counseling have been found to be effective, neither is adaptable considering the sheer volume of preclinical AD participants for the Generational Program trials, with an expected *N* of greater than 3,000 participants. The committee also noted that although the past studies reported no significant increases in depression or anxiety symptoms, the settings and populations were restrictive and not generalizable, excluding low to average income individuals and individuals struggling with underlying psychological conditions (Romero et al., 2005; Green et al., 2009; Roberts et al., 2011; Christensen et al., 2018; Green et al., 2015; Langlois et al., 2019).

The GTCD committee included "physicians, social science researchers, health educators, legal experts, and genetic counselors" with experience in AD, medical ethics, and genetic risk factor disclosures (Langlois et al., 2019, p. 707). Initially the committee was meeting every 2 weeks by phone and every quarter in-person with continued meetings monthly by phone upon design completion. Their design included the use of eight components during ApoE test disclosure and counseling: Required ApoE testing, psychological assessment for readiness, relevant risk estimates for AD, guidance to identify disclosure providers, pre-disclosure

education, ApoE materials for counseling and disclosure sessions, ApoE counseling and disclosure session flow, and ApoE assessment of disclosure impact. This model was developed in the context of clinical trials (Langlois et al., 2019).

All participants, even those with prior ApoE testing and disclosure results, were required to complete ApoE counseling and disclosure sessions, along with repeated lab testing to ensure consistency and standardization (Langlois et al., 2019). In an effort to reduce psychological risk to participants, the GTCD required that each individual was assessed for psychological readiness. The assessments given included the 15-item Geriatric Depression Scales (GDS; Sheikh et al., 1986) and the 6-item State-Trait Anxiety Inventory for Adults (STAI-AD; Marteau et al., 1992). The second generation of this study was planned to include the Columbia Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011) to assess participant's present and past suicidal ideation and behaviors. The First Generation study assessed suicidality prior to ApoE disclosure, with the exception of ApoE-ε4 positive allele participants who were administered the C-SSRS. Participants with a GDS > 6 and STAI-AD > 19 for were excluded from the Generation 1 study, while the Generation 2 study was more flexible with no cut-offs, but required investigator review for participant inclusion (Langlois et al., 2019). Participants could be excluded from the study for suicidality or monitored per trial protocol (Langlois et al., 2019).

AD risk estimates that were found during prior studies were analyzed by the GTCD committee for both MCI or dementia in cognitively normal individuals aged 60-75, separated by ApoE genotype, and these estimates were found to be extremely variable when compared with lifetime risk estimates (Qian et al., 2017; Langlois et al., 2019). Therefore, the risk estimates developed for this model were lowered from previous publications on ApoE disclosures (Cupples

et al., 2004; Langlois et al., 2019). This change also supported GTCD's decision to require all participants to complete genetic counseling and disclosure sessions notwithstanding prior ApoE knowledge or risk status (Langlois et al., 2019).

An effort to improve participant access to genetic counselors and disclosure providers, the U.S. and Canada were allowed by GTCD to use centralized, remote genetic services with offsite genetic counselors for ApoE counseling and disclosure sessions (Langlois et al., 2019). Sessions were allowed to occur over the phone or videoconferencing when in-person was impossible. Other parts of the world used local providers. Any local providers were required to be qualified by their governing agency in genetics and to be licensed appropriately. Providers without governing regulations were trained by clinical professionals. Any providers with undetermined credentials and training were reviewed by sponsors before providing services (Langlois et al., 2019).

Regarding predisclosure education materials, the GTCD created self-directed materials, including a video and brochure that cover the information usually provided during the pretesting counseling session (Langlois et al., 2019). These materials include information on the ApoE gene and its connection to AD, along with understanding one's ApoE genotype for the participants and their families. The materials also contain several multiple-choice questions and feedback explaining the correct responses. Participants should be encouraged to stay familiar with the information learned prior to their ApoE counseling and disclosure session (Langlois et al., 2019).

During the genetic counseling and disclosure session, participants are provided with materials that contain specific topics to keep the session standardized (Langlois et al., 2019).

The genetic counselors were required to utilize handouts and visual aids during session, while being mindful to stay focused on the specific topics within these materials. These topics assist in preventing any variability in providers ApoE genetic knowledge and skills when counseling and providing disclosure to the participants. Participants' attendance at an ApoE counseling and disclosure session was required for this study; however, for participants previously aware of ApoE status, the implication of and interest in knowing their status was not reviewed but was supplemented with a discussion about disclosure impact on them and their family (Langlois et a., 2019).

ApoE risk summary sheets are recorded with copies provided to each participant at the end of the session. The materials were created for easy cultural adaptation (Langlois et al., 2019). During baseline sessions, the educational content given during pre-disclosure is discussed, along with family history and feelings about ApoE disclosure and a desire to learn ApoE status. The participant is also required to again confirm a desire for ApoE status. Other topics discussed include inheritance effects, comparison risks, risk modifiers and resources available for more information. Participant's post-disclosure appointment can be completed in-person or over the phone (Langlois et al., 2019).

When assessing the impact of ApoE disclosure on participants, a test battery should be administered at 2-7 days, 6 weeks, 6 months, and 1 year after disclosure (Langlois et al., 2019). The measures for the Generation 1 study included psychological well-being measures previously mentioned, assessment of their understanding and retention of information provided the disclosure process, perceived risk and AD threat beliefs, the impact of ApoE testing, and any motivation to learn test results. The Generation 2 study had an abbreviated battery with a 2-7

day follow-up administering the GDS and STAI-AD, with post-disclosure follow-up assessments administered either over the phone or in-person. Noted is the fact that safety assessments were completed for all participants throughout the studies (Langlois et al., 2019).

As a result of this process, GTCD members have provided an alternative genetic counseling and disclosure model for ApoE to assist in providing consistency and standardization to manage the volume of information being collected and analyzed in AD research (Langlois et al., 2019). This impact data was trying to increase researchers' understanding of risks and benefits in modified disclosure counseling while informing future changes to optimize outcomes in research and the clinic (Langlois et al., 2019). GTCD suggested future model adaptations to address participants' behavioral areas of health, lifestyles, finances, employment, and any discrimination regarding ApoE status (Langlois et al., 2019).

In the past, ApoE genetic testing and disclosure demonstrated limited clinical benefit in clarifying risk, improving diagnosis/prognosis, or informing treatment. For this reason, genetic science in both 2011 and 2018 recommended against ApoE testing (Goldman et al., 2011; Goldman et al., 2018). Subsequently, insurance companies refused to pay for ApoE testing (Arias et al., 2021). However, recent advances in AD research have the potential to affect change in this area (Largent et al., 2021). Clinical research trials for possible AD treatment therapies have made ApoE testing and disclosures more frequent and normalized (Largent et al., 2021).

In 2021, a longitudinal study was created to analyze the impact of ApoE disclosure on ε4 carriers, including concerns about discrimination and changes in health and lifestyle behaviors to reduce AD risk (Largent et al., 2021). This study, referred to as the Study of Knowledge and Reactions to ApoE Testing (SOKRATES II), was part of the API Generation Program.

SOCKRATES II was aimed at obtaining qualitative data on cognitively unimpaired older adults who learned their ApoE status to enroll in AD clinical research trials (Largent et al., 2021). This study involved two generations of participants with the Study 1 generation participants required to be cognitively unimpaired, ε4 homozygotes (e.g., containing identical ε4 alleles), and aged 60-75 at baseline. The Study 2 generation of this same study had the same participation requirements, but with ε4 carriers included and ε4 heterozygotes (e.g., containing different ε4 alleles) needing an elevated amyloid-β. Overall, there were three participant groups: ApoE ε4 homozygotes, heterozygotes, and noncarriers, analyzed between Study1 and 2 time periods. (Largent et al., 2021).

Participants were part of the API Generation Program and had to have learned their ApoE status through this program to be eligible for the SOKRATES II study (Largent et al., 2021). After ApoE disclosure, API participants were provided study information and instructed to contact research staff at the University of Pennsylvania regarding their interest in SOKRATES II. The number of individuals who received recruiting materials is unknown, however, 163 individuals contacted researchers with 8 ineligible, 9 who declined, and 76 who were not interviewed because demographic quotas were full and closed to enrollment (Largent et al., 2021).

A total of 75 participants, (50 ε4 carriers and 20 non-carriers) completed interviews at 3 months and 15 months post ApoE disclosure (Largent et al., 2021). All participants generally understood their ApoE status. Non-carriers reported feelings of relief, while ε4 carriers described being “disappointed” by ApoE results but “glad to know” it (Largent et al., 2021, p. 2). The participants who were carriers reported concerns regarding possible stigmas or

discrimination. Participant carriers implemented more new health regimens than non-carriers. They also modified elements of their future to account for their increased AD risk. All participants reported hoping their research participation could assist others. The interviews were audio recorded and professionally transcribed with NVivo qualitative analysis software used during data analysis and coding. Researchers identified themes within a codebook with descriptive codes pulled from the data and interpretive information found in the literature concepts.

The Study 1 results revealed that one third of ApoE ε4 homozygotes expressed positive "empowerment" feelings, reporting that the information helped them to "prepare ahead of time…prepare for later life and make plans based upon the probabilities that I would, in fact develop Alzheimer's disease" (Largent et al., 2021, p.5). The negative emotion reported involved being "devastated, sad, and concerned," including "fears of burdening others" (Largent et al., 2021, p. 5). Another one third of ApoE ε4 homozygotes reported a mixture of positive and negative emotions indicating "I felt like a domino fell…but on the other hand it's empowering…I can contribute to the science of it" (Largent et al., 2021 p. 5). The final ApoE ε4 homozygotes reported neutral feelings of acceptance indicating it is "just one of those things" (Largent et al., 2021, p. 5). ApoE ε4 heterozygotes fell into the same three categories with positive feelings more prevalent, with hope, empowerment, and gratitude they did not have ApoE ε4 homozygote status. Their negative emotions included a "sinking feeling" about cognitive impairment (Largent et al., 2021, p. 5). One fifth of ApoE ε4 heterozygotes reported feeling a mixture of positive and negative emotions. Finally, the non-carrier participants expressed only positive feelings indicating "a weight…being lifted off my shoulders" with some still guarding

their optimism with a belief that they could still develop AD even as a non-carrier (Largent et. al, 2021, p. 5). Some non-carriers reported feelings of relief for their family members, believing it would be unlikely that their family or children carried the ε4 allele.

The study homozygote and heterozygote participants had shifted to neutral feelings of "coming to terms" with their status over the past year. They stated "it is what it is. I don't worry about it" and "I was more nervous and upset before…now…I'm more serene with it" (Largent et al., 2021, p. 6). Heterozygote participants reported a release of their negative emotions about their ApoE status, noting "there's nothing much I can do about it. So whatever happens, happens" (Largent et al., 2021, p. 6). Many of the ε4 carriers reported increased positive feelings at 1 year than during Study 1, indicating they were "happy to know what my potential exposure might me" (Largent et al., 2021, p. 6). Finally, two-thirds of noncarriers continued feeling a large amount of relief, gratitude, and happiness with the other one-third feeling neutral or "fine" (Largent et al., 2021, p. 6).

The most common change in future plans reported by carriers was financial planning, including long-term care insurance (Largent et al., 2021). Additional thoughts surrounding future housing, burdening others, and changes to leisure plans of travel and of spending time with family while cognitively normal. Three-fourths of the non-carriers denied making any changes to future plans with a small number of non-carriers reporting feeling more able to implement future plans (Largent et al., 2021).

The population studied during this research was limited In that it was not reflective of AD patients generally, with most participants expecting to carry at least one ε4 allele because of their family history of AD (Largent et al., 2021). Therefore, generalizability was limited. Further,

minority participation in this research was low, despite the fact that prevalence of AD in African American and Hispanic culture remains high. The disclosure process during this study also required a lot of time and resources, which may not be possible in many clinical settings (Largent et al., 2021).

Researchers during this study concluded that ApoE testing and disclosure have become part of disease-modifying AD treatments with an expectation to be adopted into clinical practices (Largent et al., 2021). They further posited that this research provides insight into the future patient experience for cognitively unimpaired adults who received biomarker information regarding AD. Researchers stated this work should further inform more evidence-based strategies when communicating AD genetic results to cognitively unimpaired adults. They specifically emphasized the need for providers to be sensitive to how ApoE status can shape self-perceptions and attitudes about memory, along with worries regarding stigmas and discrimination (e.g., retirement and effects on family; Largent et al., 2021).

CHAPTER IV: ETHICAL CONSIDERATIONS

Ethics in Genetic Testing and Human Genome Sequencing

Human genome sequencing has created an era of genetic discovery and a progressively growing understanding of disease and illness (Burke, 2014). This increased demand for genetic testing has put clinicians in a situation where they are tasked with deciding the appropriate tests to select in this process. In human genome sequencing, there are three categories of test performance (e.g., reliability and validity) that need ethical consideration, 1) analytical validity, 2) clinical validity, and 3) clinical utility. The first category, analytical validity, involves how accurately a particular gene is identified during gene testing, commonly referred to as its reliability. The second category is clinical validity, which pertains to how accurately the genetic test properties identify a patient's clinical status. The final category, clinical utility, examines the risks and benefits of genetic test use.

Understandably, the level of accuracy and contribution to improve health outcomes varies from one genetic test to another. Outside variables can also affect clinical validity and utility, such as genetic testing technology and the clinical setting (Burke, 2014). However, the APA code of ethical guidelines and standards require that clinicians thoroughly examine these categories regarding genetic testing and human genome sequencing (APA, 2017).

The prediction ability of genetic tests is an important part of clinical validity. Genetic tests assist clinicians in reliability by either confirming or refuting a possible diagnosis (Burke, 2014). In this regard, clinical validity has been used to describe how accurately a genetic test can identify a specify condition. This process is ethically connected to Principle A of the APA Code of Ethics and Standard 3.04 requiring clinicians to allow no harm or do no harm (e.g.,

nonmaleficence) to patients (APA, 2017). While confirming a genetic test's clinical validity, many variables are involved and analyzed such as sensitivity, specificity, positive predictive value, and negative predictive value (Burke, 2014). The positive and negative predictive values of a genetic test assists clinicians in determining a test's reliability level. Penetrance of the genetic test is also important in this process. Penetrance is the measurable proportion of individuals carrying a specific gene variant that expresses an associated trait. Typically, the levels of genetic test sensitivity and penetrance have been found to equally correlate with the levels of positive and negative predictive values (Burke, 2014). However, it should be noted that prevalence of a disease within the testing population strongly influences positive predictivity (Burke, 2014). Therefore, APA ethical guidelines require that clinicians involved in genetic risk disclosure apply the ethical factors mentioned above during their work (APA, 2017).

Sensitivity is another category that is reviewed regarding genetic testing. Genetic mutations can result in limitations in sensitivity (Burke, 2014). This can cause a very high positive predictive value and a limited negative predictive value (e.g., false positive). Another influence on sensitivity is ethnicity. For example, a patient in an ethnic group with limited genetic test sensitivity can have a very high negative predictive value (e.g., false negative). Finally, genetic sequencing methods can enhance diagnostic sensitivity. However, in some cases, genetic sequencing involving multiple genes can detect more variation than single gene sequencing, which could result in increases false positives or false negatives. As a result, some sequencing may also result in findings with an uncertain clinical significance or findings that are difficult to interpret (Burke, 2014).

The final category that is reviewed in genetic testing is clinical utility, which involves the risks and benefits resulting from using these genetic tests (Burke, 2014). This concept is also covered in Principle A of the APA Code of Ethics addressing beneficence (APA, 2017). The important questions to consider when reviewing clinical utility include: 1) does the genetic test and interventions lead to improved health outcomes for those with positive results? and 2) what risks happen due to genetic testing? (Burke, 2014, p. 6) In order to thoroughly evaluate clinical utility, a review of a patient's medical and social outcomes in regard to the testing and interventions needs to be explored. Reviewing the outcomes for those receiving versus those who have not received subsequent intervention is very helpful. One of the best ways to measure this is through clinical trials that measure treatment outcomes, comparing recipients with nonrecipients (Burke, 2014).

Unfortunately, genetics can be difficult when it comes to measuring these outcomes due to the varying test accuracy and contribution to health results (Burke, 2014). Specifically, the ApoE genetic risk test has been a well-established clinical utility for identifying an individual's risk factor for developing AD. In 2017, Sabbagh et al. found that this biomarker helped to improve the clinical diagnosis of AD from 55% to 84% accuracy.

However, it should be noted that the presence of these ApoE genes only indicates susceptibility to AD, not diagnosis or etiology (Atkins et al., 2011). The identification of the ApoE susceptibility genes provides little clinical utility diagnostically as an individual may carry the ApoE- ε4 allele and never develop AD or an individual may not carry the ApoE- ε4 allele and develop AD. For this reason, diagnosing AD creates clinical challenges and demands clinical expertise beyond ApoE genetic testing and genetic risk disclosure. When diagnosing AD

clinicians cannot rely only on genetic testing but should utilize several resources (e.g., patient/collateral interview information, medical history, family history, imaging, lab results, and clinical observations; Atkins et al., 2011).

Additionally, as AD research has progressed, clinicians have identified additional biomarkers to help detect this disease, especially in individuals with MCI who may develop AD in the future (Caprioglio et al., 2022). A 2020 research study was recently completed utilizing surveys sent to several memory centers throughout Europe ($N = 150$). The questionnaire was divided into ten sections: respondent's professional information, request for contacts of specialty clinicians at the memory clinic, beliefs about pathogenic role of tau and amyloid in AD, respondent's clinic work, frequency of use with biomarkers (e.g., MRI, PET, CSF), use of biochemical biomarkers in clinical reports, diagnostic added value of biomarkers, clinical vignette asking responders to rate diagnostic confidence based on abnormality of biomarkers, and perceived clinical utility of amyloid-PET and tau-PET. This survey involved two steps with the first being contact with clinicians working at the memory clinics, asking them to provide contact information for specialty clinicians working in nuclear medicine, radiology, and clinical laboratories. The second contact involved surveying the specialty clinicians identified during the first contact (Caprioglio et al., 2022).

Overall, 150 surveys were completed during this study (Caprioglio et al., 2022). The surveys were assessed by researchers in the following areas: 1) belief about the role of amyloid and tau in AD symptoms and pathology, 2) the volume AD biomarkers used with MCI patients, 3) the volume of use of AD biomarkers in etiological diagnosis of MCI cases, 4) the value of FDG-PET, CSF, amyloid PET and tau PET versus neuropsychological testing and structural MRI

in MCI cases, 5) the level of confidence in diagnosing MCI due to AD based upon AD biomarkers, and 6) responders, passive perceived clinical utility of amyloid-PET versus tau-PET in MCI and mild dementia cases (Caprioglio et al., 2022). The final sample reviewed included 100 clinician and 37 biomarker experts (9 radiologist, 18 nuclear medicine physicians, and 10 laboratory physicians) with 45% being head of their memory clinic. These clinicians were estimated on average to see 13-17 new MCI patients each month. The survey was the largest interdisciplinary survey regarding use and perceived utility for AD biomarkers on MCI cases (Caprioglio et al., 2022).

The researcher's analysis revealed a predominant role for amyloid versus tau with perceived clinical utility for PET scans, but no difference in preference between amyloid-PET or tau-PET (Caprioglio et al., 2022). During clinical assessment of MCI cases, the most used biomarkers for determining medio temporal lobe atrophy (MTA) were MRI then CSF. Biomarkers for AD hypometabolism were FDG-PET, amyloid-PET, and then tau-PET. Clinicians and biomarker experts considered amyloidosis and neuronal injury the most convincing biomarkers for AD with MTA alone seen as less reliable. Overall researchers discovered that cerebrospinal fluid (CSF) is currently believed to have the most useful clinical utility when assessing AD in MCI patients (Caprioglio et al., 2020).

Similar to clinical validity, clinical utility includes several important variables such as study size, selection criteria, lab assay, outcomes measured, and compared cases or controls (Burke, 2014). Study designs analyzing utility have to look at more than just the intervention; they must include the disease process and anticipated benefits and cannot be limited to medical outcomes alone, which are insufficient for determining a genetic testing's clinical utility. Other

factors such as testing and treatment access, appropriate referrals, service costs, patient treatment acceptability, and social consequences of genetic testing influence research results and need to be considered within study designs. Further, genetic tests that are highly predictive tests are not likely to be questioned regarding clinical utility, however, less predictive tests may face more controversy in this area (Burke et al., 2010). For example, ApoE genetic testing identifies individuals with an increased risk for AD. Past smaller studies have revealed that a positive ApoE test result can result in purchases of long-term care insurance and preparation with family members, but also, might cause emotional upset and increased psychological distress. These different responses highlight the possible benefits and the risks associated with genetic testing beyond the medical outcomes. One genetic testing area that has focused beyond medical outcomes involves the moral conflicts within reproductive genetics and decisions regarding pregnancy termination. An example of this would be the debate regarding Downs Syndrome genetic testing during pregnancy. Another example would be genetic testing during pregnancy within a family to determine if that pregnancy can provide bone marrow for an ill sibling. These examples confirm that society legitimacy is an important factor during prenatal genetic testing (Burke et al., 2010).

Further, the research methods used to study genetics need to be both quantitative and qualitative to get an accurate measure of clinical utility of genetic testing and human genome sequencing (Hayeems et al., 2020). Early conceptualizations of clinical utility in genetic testing came from the Centers for Disease Control (CDC) with the definition being the balance of benefits and harms when using tests in clinical practice to improve outcomes or add value to the decision-making process (Hayeems et al., 2020). Over time, this original clinical utility model

developed into four groups: diagnostic and prognostic ideas, therapeutic choice, patient impact, and familial and society impact. Currently the clinical utility model has expanded further into patient focused definitions of clinical utility, including those beyond drug selection and health outcomes such as the psychological and social effects on the patient and his/her family (Hayeems et al., 2020).

Ethics in Genome Sequencing/ Testing – Public Health versus Prevention Health

In 2016, a literature review of 299 articles was performed to assess the ethical, legal, and social issues surrounding the current research that was investigating personal genomic medicine (PGM; Callier et al., 2016). This research review included two independent reviewers who examined scholarly articles from 2008 through 2012. The review sought to capture a wide variety of information on ethics in PGM, exploring medical, social science, philosophy and bioethics databases. The authors searched databases with key word terms including but not limited to genetic testing, genetic counseling, genetic, biomedical research, genomics, genetic variation, genetic research, legislation, jurisprudence, research, and ethics. Bioethics articles were subsequently searched similarly and integrated into this review. The method of review used involved identifying key issues and adding them to a coding list that was then further categorized into themes and refined through the review process (Callier et al., 2016).

During their review of the ethical, legal, and social implications (ELSI) of research within this timeframe, analysts discovered that the predominant focus of genome research pertained to consent, disclosure, data sharing, privacy, and confidentiality (Callier et al., 2016). They further noted a definite shift in ELSI topics due to advancing technology, which resulted in disclosure and data sharing remaining at the forefront of the research in existence. The reviewers

posited that as genomic research evolves, more precise medicine studies beyond the topics of disclosure and data sharing are expected. In this regard, they discussed a need for more diversity among research participants, including a clearer definition of race and ethnicity and an understanding of the need for a more globally diverse research population. Further, their review indicated that precision medicine research is anticipated to pursue specific genetic properties and medical therapies aimed at targeting conditions such as cancer or earlier identification of conditions such as heart disease and Huntington's disease. They asserted that ELSI research specific to certain medical conditions has the potential to positively affect research participants' experiences. Finally, some other areas the reviewers felt were not adequately represented were participants suffering from mental health issues or substance abuse, and participants in different age groups. The importance of understanding ELSI issues specific to a population being studied was reinforced by reviewers to ensure that research studies occur appropriately. Another ELSI issue the reviewers' analysis discovered was the importance of translating research into clinical care. Specifically, the importance of clear research guidance for medical entities in disclosing and marketing the details pertaining to personal genetic risk information (Callier et al., 2016).

Based on their review, the analysts concluded their work had reinforced the importance of ELSI research literature as precision medicine evolves (Callier et al., 2016). They again mentioned the importance of having diverse ELSI research so that clinical recommendations could translate globally and beyond the typical European ancestry of the past. They also expressed a need for genome research to involve a balance that is both broad yet following specific ELSI population guidelines (Callier et al., 2016).

In 2018, the advances in genome sequencing created new possibilities in preventative genomic sequencing, as screening programs created a crossroads between public health and preventative health (Morrissey & Walker, 2018). Naturally, clinical ethics and public health ethics are at the forefront of this debate, which centered around concerns for individual rights. In 2018, Morrissey and Walker completed a review that examined "the right not to know" (RNTK) and a child's right to an open future.

Article 5(c) of UNESCO's Declaration on the Human Genome and Human Rights defines the RNTK as one's right to determine "whether or not to be informed of the results of genetic examination and the resulting consequences should be respected (Lenoir, 1997; Morrissey & Walker, 2018, p. 27). Morrissey and Walker (2018) felt it was important to separate the "right to know" information from the RNTK genetic information. They described this difference as access to important medical decision-making versus freedom from specific types of medical information. Even though an individual's right to medical information is not debated in medical ethics and the informed consent doctrine, there is frequent disagreement about these rights in actual medical practice. These researchers emphasized that a RNTK needs to be understood as "a right against being informed of particular types of information, in specific circumstances, by particular other persons or institutions" (Morrissey & Walker, 2018, p. 27). The implications of RNTK includes a medical professional's duty to avoid presenting information to individuals who do not want it to be disclosed. RNTK tends to occur most frequently regarding information of genetically predisposed conditions that may harm an individual's life socially or psychologically (Morrissey & Walker, 2018).

In 2013, the American College of Medical Genetics and Genomics (ACMG) proposed that RNTK conflicts with the physician's ethical obligations of beneficence and nonmaleficence, specifically regarding disclosure (Morrissey & Walker, 2018). ACMG was departing from the patient autonomy of RNTK by adhering to the belief that clinicians have a fiduciary duty to prevent harm by disclosing findings to patients and families (Green et al., 2013). However, feedback responses from ACMG members in 2014 resulted in a change back to supporting autonomy and the individual's RNTK even for genetic information that is medically actionable (Morrissey & Walker, 2018).

Despite this ACMG shift, the debate between prevention health and public health continues. An examination of this matter was explored considering children screened for adult-onset conditions such as the BRCA breast cancer risk genome (Morrissey & Walker, 2018). The reviewers addressed the fact that screeners done with children who are unable to make their own choice essentially takes their choice away (e.g., taking away their RNTK). In these cases, one's RNTK would be considered justified in that children themselves are not able to decern whether or not such medical information assists or deters one's own well-being. However, children's parents and the community rights overall were explored by reviewers through a social justice lens seeking a deeper understanding of the RNTK regarding genetic information and testing. They mentioned a potential expansion of individual rights into community rights. For example, they analyzed a child's right to a future with unlimited access to healthy goods and services. Although one's RNTK is related to an individual's future wishes, this decision not to know is determined by the information available to each individual. For example, if parents are well-informed and pro-active, they may tend to be exposed to current preventative genome

sequencing (PGS) information when making their child's RNTK decisions. Social justice would promote the community (e.g., physicians, parents, and public health agencies) to provide information about medically actionable genes (MAG's) to the general population. This could include regularly offering PGS to patients in the primary care setting for patients without symptoms or a family history of disease including newborn screeners, child physicals for starting school/sports, or even preconception carrier screenings (Morrisey & Walker, 2018).

The conclusion reached by reviewers was that individual rights such as the RNTK and a child's right to an open future may need to be interpreted individually (e.g., case-by-case) and promoted within the context of preventative genome sequencing (PGS; Morrissey & Walker, 2018). They also determined that an individual's rights within the areas of clinical and public health should be determined while including a social justice view if one is to accurately perceive all the ethical dimensions of the general population PGS's (Morrissey & Walker, 2018).

Ethical Issues in ApoE Disclosure and Counseling

Beneficence

Genomic sequencing has recently experienced a radical shift, distancing itself from the medical principles of minimization (Prince & Berkman, 2018). Previously the understanding of potential risks and benefits have been centered around prior psychosocial studies pertaining to targeted genetics. The authors assert that the current genomic era requires that the past perception of risks and benefits need to be re-evaluated to see if they have held up over time with the advances in the clinical field and the changes in technology. Genetic information is more available now and has been slowly changing the viewpoint on the risk and benefits of genetics and genetic testing. Single gene testing will continue to be utilized in research, but consideration

must be given to how the harms and benefits may be changing for gene sequencing studies. This analysis of beneficence not only provides insight for researchers and clinicians, but also for the Institutional Review Board (IRB) when evaluating research studies (Prince & Berkman, 2018).

Further, in 2020, researchers analyzed disclosure strategies in three Western countries (e.g., U.S., Canada, and Germany) to identify any limits in existing ethical guidelines (Alpinar-Sencan & Schicktanz, 2020). Biomedical research is continuing to increase, creating even more of a need for ethically appropriate ways to disclose genetic information. Participants in research are some of the most important sources of information within the biomedical field (De et al., 2021). The Declaration of Helsinki protects the well-being of research participants by prioritizing ethical research over any advancements in society and science (World Medical Association, 2001). Some ethical genetic disclosure methods include providing adequate information and support through genetic counseling, seeking to know the participants' perceived concerns, and collaborating regarding ongoing ethical discussions. Further, in 2021 researchers noted the study participants who preferred to disclose their ApoE information to family may gain emotional support from them, including help with healthy lifestyle changes. These researchers also surmised that this desired level of participant involvement creates collaborators in the genetic disclosure process (De et al., 2021).

Technology has provided the ability to gather significant amounts of information about individuals who decide to participate in genetic testing (Prince & Berkman, 2018). The current era has evolved into expansive genetic testing for a variety of genetic information, generating much more genomic sequencing for participants. As this information continues growing and changing, so will the concept of beneficence. This sequencing has the benefit of providing

unlimited information about individual testing, but it also has the potential to alter how view risks and benefits are viewed (Prince and Berkman, 2018).

Confidentiality and Privacy

The recent technological improvements in genetic testing and analysis have promoted a substantial increase in human genome information (Clayton et al., 2019). This increase has also created a diverse array of involved individuals, patients, and genetic data, causing difficulties in developing broad enough legal principles to maintain genetic privacy. Since the beginning of these debates decades ago, the issue of balancing individual rights of privacy (HIPPA and GINA) with other's rights and societal interests remains in the forefront. While conducting genomic research, a balance between these two essential needs must be attained: 1) the need to share data openly to increase ongoing scientific knowledge within society, and 2) the need to protect each research participants' individual privacy. In an effort to support this balance, federal laws including HIPPA, GINA, and The Common Rule were created to both promote our progress in science while still protecting patient privacy (Clayton et al., 2019).

One challenge within confidentiality and privacy is attaining true patient anonymity, as each individual's DNA is unique. This issue was addressed during a 2013 research study that examined the effectiveness of using surnames to de-identify patient genetic information (Gymrek et al., 2013). The goal was to explore how simple it would be to expose surname inferences from public information on the internet, specifically, internet searches on recreational genetic genealogy databases. The data resources used included the two largest free public genetic genealogy databases that allow searches based upon genetic similarities and allele combinations (e.g., www.ysearch.com and www.smgf.org). This dataset included 39,000 unique surnames

from 135,000 records. Researchers tested the integrity of known surnames by querying their connection to 34 biomarkers from 911 individuals and 521 surnames. This was possible because genomic science would frequently share data without identifiers (e.g., surnames), resulting in easier access and recovery of surnames through the internet by profiling and querying genetic genealogy databases. The algorithm(s) created further assisted researchers who created several search methods with only limited information such as birth year and surname or religious ancestry and surname. Researchers in this study were able to connect this information with the correct biomarker information with 99% accuracy in most cases. During this process, the data also revealed that a release of only a few biomarkers can spread throughout shared genealogy connections, making it simple to identify similar genetic features from others' information as well. Researchers expect this surname inference issue to only increase in the future considering the growing use of technology in genetic research (Gymrek et al., 2013).

The researchers concluded it did not matter what surname was used or what patient information the surname was tied to because the large volume of information shared on websites and mailing lists prevents true anonymity (Gymrek et al., 2013). They decided this surname method was impractical and suggested implementing controlled access of databases and use agreements to help limit the surname inference regarding genome information. Unfortunately, this suggested termination or limiting of data sharing would also be devastating to scientific progress with the sole goal of improving human health and decreasing disease. Eventually, these researchers determined that establishing clearer policies pertaining to sharing data, educating gene testing participants, and legislating the proper use of genetic information is crucial in facilitating continued progress of human genomics and patients' privacy (Gymrek et al., 2013).

In fact, the National Human Genome Research Institute (NIH) has established control access to sensitive or potentially identifiable information within these databases to assist in respecting research participants privacy (NIH, 2023). Certificates of Confidentiality are also issued to afford NIH-funded researchers the ability to limit access to participants' health information (NIH, 2023).

Maintaining confidentiality with more complex genetic testing can be increasingly difficult when a combination of genes are included in the disease risk factor, such as ApoE genomes measuring one's risk of AD (Nyholt & Visscher, 2009). In this case, ApoE genetic risk factors are indirect estimates relevant to confidentiality, discrimination, defamation, and informed consent for the recipient and their relatives. However, HIPPA was never intended to provide privacy protection for the volume of genetic information currently being created, stored, shared, and analyzed (Clayton et al., 2019). Even when all this information is stored in a HIPPA compliant manner, the sheer volume of exceptions and compelled disclosures prevents privacy and confidentiality (Clayton et al., 2019).

Genomic population research and genetic testing are frequently pulled from biobank repositories and accompanying databases during the matching process, which can make genomic research potentially identifiable (Witt & Witt, 2016). Essentially, the ability to maintain one's anonymity proves to be inherently untrue. One way to minimize the impact on confidentiality involves proper use of the informed consent to protect participants' autonomy (Witt & Witt, 2016).

Further complicating the matter are the unique features that differentiate genetic information from other healthcare data (Witt & Witt, 2016). For instance, many genetic traits are

connected to family members and may lead to psychological fatalism, discrimination, social stigmas, and overall insecurities encompassing life. This data requires heightened security due to the sensitive personal data it contains, however, it may also increase the potential danger of a confidentiality breach (Witt & Witt, 2016).

Although human genome knowledge and insight is increasing, the issue of confidentiality remains complex and difficult (Witt & Witt, 2016). Determining how strictly confidentiality should be reinforced within genetics is still very unclear. Similar to any medical data, confidentiality is the basis for patients' and donors' confidence and trust. However, there are some cases in research in which it is not possible to return the results to the patients or their family (e.g., rare diseases). In fact, much genetic data is very subjective and individualized, requiring a case-by-case approach when it comes to confidentiality (Witt & Witt, 2016).

One approach to gain more insight into the area of confidentiality involves questioning participants about their level of concern regarding the use of their genetic information. A recent study done in Finland sought to better understand participants' perceptions regarding confidentiality (De et al., 2021). This study involved 281 participants who were provided with a closed-ended questionnaire regarding their perceived concerns. Out of these 281 participants, 89% (n = 250) answered the independently created questionnaire. All participants were native Finnish citizens with an age range from 27 to 72 years old. Interestingly, only 6% of participants reported concern about the possible use of their genetic information in other projects. The main concern identified by participants in this study was the potential distress for family members and relative regarding disclosure of their genetic predisposition to AD. In fact, an important finding in this study was that 87% of these participants preferred their susceptibility information be

shared directly by them and not their doctor. A further conclusion during this study was that this method of disclosure to family and relatives would allow participants to gain emotional support and support for changes in lifestyle. These same participants revealed little concern regarding their health information being discovered by employers or insurers, with no anticipated negative consequences (De et al., 2021).

Integrity and Competence

Currently, healthcare providers' use of human genetics, genetic testing, and genetic disclosure as disease prevention and treatment biomarkers is exponentially increasing (Owusu Obeng et al., 2018). Clinical care has been stimulated by genetic data combined with advanced technology regarding human health (Owusu Obeng et al., 2018). Genomic medicine promises to optimize risk prediction diagnostically, while assisting with the prevention and treatment process clinically. Genetic information has provided a continuous expansion of the ability to diagnose and predict disease. The majority of treating physicians believe in genomic medicine's clinical use but may not be adequately trained (Owusu Obeng et al., 2018).

Owusu Obeng et al. (2018) surveyed 285 physicians from five different sites. The surveys were administered from 2014 to 2016 and were designed from medical literature using queries and site characteristics. Prior to this, the researchers' survey instrument was tested with a small number of physicians and investigators at several sites and their feedback helped with revisions (Owusu Obeng et al., 2018). The survey was then administered either in person or electronically with generic questions customized to each site without a loss of the underlying theme. Of the 285 physicians surveyed, 73% came from two disease gene projects and 27% came from three pharmacogenetic projects. Approximately, 79% of the physicians at

pharmacogenetics sites had been in practice for 1-5 years and 69% of the physicians at disease genetic sites had been in practice over 5 years (Owusu Obeng et al., 2018).

This study further confirmed what past studies had discovered, that physicians believe genetic information is relevant but the skills and knowledge to effectively implement genomic medicine into their practices is absent (Owusu Obeng et al., 2018). The physicians also believed that their medical training left them unprepared for practicing genomic medicine, lacking in confidence to share genetic information with patients, and without adequate resources regarding genetic tests. Specifically, only 15% felt confident to use genetic information in their practice, with two-thirds of physicians agreeing genetic testing was relevant but only one-third believing access to genetic testing information would improve their patient care. Further, only 23% of physicians could locate the resources they needed to implement genetic testing within their practice. This study also revealed a significant difference in the attitudes and perceptions of physicians depending upon their setting. For example, physicians working with pharmacogenetic testing felt more confident and prepared in their abilities than physicians who worked with genetic testing for disease. Physicians with more years of practice were also found to be more supportive of genetic medicine's clinical utility (Owusu Obeng et al., 2018).

As a result of the data obtained during this study, researchers concluded that identifying other items to help support increased implementation of genetic testing resources would be important (e.g., peer-reviewed guidelines, alternative therapies, and implementation tools; Owusu Obeng et al., 2018). Researchers did note a pattern of and increased comfort with genetic testing among newly graduated medical students, specifically feelings of confidence in incorporating genetic information into their clinical decision-making. They concluded that prior

experience in genetic testing appeared to have influence on the physicians' level of genetic understanding, but the majority of physicians within this sample were not yet able to access this resource within their practices. Researchers reinforced the importance of discovering and addressing the current barriers hindering clinical implementation of genomic medicine. Specifically, they suggested implementing interactive and practice-based training and educational programs for practicing physicians (Owusu Obeng et al., 2018). One area for this practice-based training and education could include the creation and implementation of interdisciplinary teams with clinical psychologists trained in research and clinical practice regarding human genetics.

Physicians are not the only clinicians experiencing this lack of resources and training. Individuals with access to their genetic information about their future health creates an increased need for therapeutic services from psychologists. In response to this demand, psychologists need to be prepared to provide ethical and effective treatment to individuals processing this genetic information (Richmond-Rakerd, 2013). Essentially, psychologists need to increase their literacy regarding genetics (Guttmacher, 2001). Currently, the best resource for this information comes from The National Coalition for Health Professional Education in Genetics, along with an APA specialty organization who created a set of core competencies within the genetics area for healthcare workers which was revised in 2007 (Jenkins et al., 2001; Richmond-Rakerd, 2013). The revision in 2007 included an additional level of training for professionals providing genetic counseling services (Richmond-Rakerd, 2013).

While providing care in genetics, psychologists are faced with many issues: "1) values conflicts and value system disparity, 2) confidentiality, privilege, and recording keeping, 3)

informed consent, and 4) competence and training issues." (Richmond-Rakerd, 2013, p. 1). These issues are relevant not only to psychologists practicing within and outside the medical setting, but also, psychologists involved in genetic research, education, and policy. The genetic counseling process is an integration of interpreting familial risk and medical history, along with education on resources, management, prevention, and research. It is meant to provide individuals with enough information so they can make an informed decision. In that regard, genetic counseling is viewed as part of genetic testing and only meant to occur for a few sessions and sometimes a single session. However, individuals who receive genetic testing may need practicing psychologists to provide them with a safe place to process any persistent distress (e.g., depression and anxiety) and gain a deeper understanding of their genetic risk and their family's risk. Internal conflict pertaining to obtaining genetic testing or sharing genetic risk with others may also require the assistance of psychologists (Richmond-Rakerd, 2013).

A psychologist's objectivity may be tested when working with an individual either debating genetic testing or processing through their genetic risk results (Richmond-Rakerd, 2013). The psychologists' own values and biases could influence the therapeutic relationship by limiting the client's autonomy. Some areas of the genetic testing debate could perpetuate a misalignment between the psychologist and client, including differing opinions on genetic risk discrimination by health insurance, ownership of genetic material, child genetic testing consents, or concerns that eugenics used to create a pure human gene pool. Strong viewpoints of the psychologist, whether they align with the client, can negatively impact the nature and outcome of the therapy relationship if gone unchecked (Richmond-Rakerd, 2013).

Many psychological studies in the areas of cognition, communication, and decision making have discovered that participants' expectations, emotions, and biases when faced with complex and uncertain information can shape patient-provider comprehension and communication (Khan et al., 2015). Important factors for psychologists to consider include participant's literacy, their information preference, their perception of current health, and their view of the providers. Also, the participant's variations in communication or preferred coping methods should be considered when the psychologist communicates sequencing information (Khan et al., 2015). Psychologists remaining aware of how their values influence the therapeutic process is required by several APA ethical principles (Richmond-Rakerd, 2013). These APA ethical principles make practitioners responsible for understanding and minimizing biases within the therapeutic process. For example, the APA ethical principles D and E pertain to 1) justice and 2) respect for one's rights and dignity (APA, 2017). They require that psychologists prevent their biases from either condoning or leading to unjust practices and require that psychologists always honor the client's autonomy (APA, 2017). The clients' pursuit of their wants and needs should exist without any psychologist influence (Richmond-Rakerd, 2013).

Essentially, psychologists can only practice ethically and in a genetically informed manner if they can identify and acknowledge their own genetic testing ideals/biases, assess the affect such ideals/biases have on clients, and work to change/minimize their influence in the process (Richmond-Rakerd 2013). This also applies to psychologists working in education and research, as their influence can affect policy, regulations, and empirical research (Richmond-Rakerd, 2013).

The ethical issue of confidentiality and privacy regarding genetic information can cause psychologists some unique challenges (Richmond-Rakerd, 2013). For instance, the conflict between protective factors for clients and their decision not to disclose their genetic risks to family members may cause conflict for treating psychologists. The psychologists' view of autonomy for the client's relatives may be in conflict with what the individual client desires for them. A client's desire may be seen by the psychologist as disrespectful and harmful to the relative's possible autonomy, in that it prevents any pursuit of genetic testing for family. The type of disease being genetically tested can also increase the level of conflict for the psychologist, as unfortunately some diseases have a genetic guarantee (e.g., Huntington's disease). APA Code Standard 4.05 on disclosures requires that psychologists may only disclose confidential client information without consent when they are protecting the client, themselves, or other individuals from harm; otherwise, client information must be kept confidential (APA, 2017). Overall, the standard for medical professionals is similar in that, other than in extraordinary circumstances, confidentiality is to be protected (Richmond-Rakerd, 2013). Regarding genetic disease risk for family members, this standard of disclosure can extend to psychologists. APA Code, Standard 4.01 pertaining to confidentiality requires psychologists to "take reasonable precautions to protect confidential information through or stored in any medium, recognizing that the extent and limits of confidentiality may be regulated by law or established by institutional rules or professional or scientific relationship." (APA, 2017, sect. 4) Overall, psychologists' primary responsibility is to their client and maintaining their privacy and confidentiality; but educating their clients regarding the potential outcomes of family disclosure is equally as important. This education includes learning any potential harms from sharing

genetic risk status and being aware of any relatives who prefer not to receive genetic risk information. This process should help clients become more capable of making informed decisions regarding disclosure of genetic risk status and prepare them for all the possible outcomes. With these guidelines, psychologists would be honoring the APA ethical code that requires preservation of trust and confidence in the therapeutic relationship, while supporting the client's self-determination and autonomy (Richmond-Rakerd, 2013). Further, when psychologists are assisting a genetic testing client in a couples or family setting, ethical Standards 10.02 for couples therapy and 10.03 for group therapy (APA, 2017) should be followed. They require that the psychologist clearly discuss the roles, responsibilities, and limits of confidentiality for all parties at the onset of any therapy (APA, 2017).

When it comes to sharing a clients' genetic information with other medical professionals, psychologists are bound by APA ethical Standard 4.05 (APA, 2017), which indicates that an appropriate client consent is needed prior to sharing any client information (Richmond-Rakerd, 2013). Additionally, the client must be fully aware of the type of information that will be disclosed, including genetic test results. The client must also be provided with an opportunity to decline any sharing of information. Psychologists must also provide the client with an informed consent as required by APA ethical Standard 3.10, wherein the client decides the type of information to be released (APA, 2017). Further, APA ethical Standard 6.01 requires that psychologists only share client information concerning their work. Finally, regarding any transferring of client information, psychologists are required by APA ethical Standard 6.02 to maintain client confidentiality records (APA, 2017). This includes electronic genetic data being

de-identified and securely coded to prevent access by any unauthorized entities (Richmond-Rakerd, 2013).

Initially, The National Coalition for Health Professional Education in Genetics created a set of competencies in the field (Richmond-Rakerd, 2013). The APA subsequently published these competencies, along with a revision which was made available in 2007 (APA, 2007). They include competencies at a basic level for all providers and a specialized level for professionals providing genetic counseling and other services. The more specialized professional is expected to understand the benefits and risks of genetic information and the importance of its sensitivities in genetic testing, disclosure, and counseling. Psychologists providing genetic services currently may need modifications to these competencies to assist in their preparedness to work in the genetics field. Although psychologists possess skills such as empathy and warmth to support a strong therapeutic alliance, specific knowledge of the genetic testing population is needed for appropriate therapy techniques and interventions. This knowledge is typically gained through the appropriate training. APA ethical Standard 2.01 requires that psychologists only practice in their areas of competence, based upon their education, training, supervision, consultation, academics, or professional experience (APA, 2017). Also, psychologists planning to provide care in a new area must also obtain relevant training or experience in that specialty area prior to providing any care (e.g., genetics; Richmond-Rakerd, 2013). Competence demands more than just mastery of relevant issues and problems, but also includes critical thinking, judgment, reflection, and self-modification. For example, a psychologist competent to work with genetic testing clients would have the clinical skills in human genetics and the ability to adapt their skills to the genetic testing population. Further, these skills need to be firmly set in ethical principles where the psychologist

understands the impact of value systems, confidentiality, informed consent, and competence regarding human genetics. This also means that psychologists acknowledge their limitations and work towards expanding their skills and knowledge in the speciality area (Richmond-Rakerd, 2013).

Further, APA code of ethics requires that psychologists recognize their level of competence and educate themselves in specialty areas where standards for practice and education do not exist yet (APA, 2017; Richmond-Rakerd, 2013). Although creating training protocols in a newly emerging specialty field may seem overwhelming, steps to help future clinicians improve their competence are necessary and required. Specifically, Standard 2.01 of the ethical code pertaining to "Competence Boundaries" requires that psychologists ensure competence so that they are protecting clients from any harm (APA, 2017).

Disclosure - Approach

Recently, genetic studies regarding dementia have gained a significant amount of attention (Alpinar-Sencan & Schicktanz, 2020). Further, research in this area has experienced a shift from cure to prediction and prevention. AD and dementia have been reconceptualized as a disease that develops over time with a preclinical phase and a slow and steady pathological phase. The use of biomarkers has been assisting clinicians in identifying each of these stages, with the preclinical stage of AD sometimes appearing as a symptomatic state of MCI and eventually evolving into a clinical disease like AD. As research has evolved in this area, there is more and more of an emphasis on preventative lifestyle interventions. This shift in focus emphasizes the importance of guidelines and recommendations pertaining to the ethical disclosure of dementia risks that can help to improve care at each stage of the disease. The

disclosure and methods for communicating genetic risks to patients need to be integrated with dementia strategies focused on disease prediction and prevention (Alpinar-Sencan & Schicktanz, 2020).

Fortunately, during past clinical experiences, several disclosure strategies have been discovered to help establish suggestions for ethical disclosure guidelines. For example, in 2018, the updated U.S. National Plan regarding Alzheimer's disease identified a failure to diagnostically disclose or provide adequate counseling and support as "a problem." (Alpinar-Sencan & Schicktanz, 2020, p. 3). In this situation, one of the strategies recommended was the need to educate physicians and other care providers in this area (Alpinar-Sencan & Schicktanz, 2020).

Another issue pertaining to genetic disclosure includes a fear of passing on the disease and the negative affect risk disclosure may have on the individual's decision to reproduce (De et al., 2021). An individual's receipt of genetic testing information can potentially result in harm such as feelings of distress, guilt, anxiety, or depression. The disclosure of genetic test results, if done unethically or inappropriately, can also cause discrimination at work or while obtaining health insurance (De et al., 2021). Therefore, ethical guidelines in the areas of beneficence and the duty not to harm (e.g., Principle A and Standard 3.04) should be integrated into the disclosure approach for genetic testing (APA, 2017).

To further explore ethical disclosure methods regarding ApoE allele status, 250 research participants from hospitals, universities, and institutes in Turkey and Finland were randomized into two groups (De et al., 2021). The first group was the intervention group who received their ApoE allele status, and the second group was the control group who was able to request

information on their ApoE allele status after the study was complete. The study lasted a year and a half. During this time, participants were given genetic counseling letters and articles, along with a questionnaire exploring their knowledge of genetics and their opinion on disclosure of genetic information, as researchers wanted to better understand the participant's knowledge and perception during the ApoE disclosure process (De et al., 2021). All participants were given a close-ended questionnaire with three main purposes: 1) knowledge of genetics, 2) participation concerns, and 3) opinions on disclosure information. This questionnaire involved a point scale to assess knowledge assessment and any concern. The three-point Likert scale where 1= *correct*, 2= *do not know*, and 3= *incorrect/disagree*. The questionnaire was based upon previous literature, with changes made by research groups (De et al., 2021).

This study discovered that over 90% of participants had no concern regarding the use of their genetic information (De et al., 2021). The two main concerns of participants, comprising approximately 10% of the sample, were the perceived stress of a genetic predisposition towards AD and the stress of potential disclosure of this information to their family (De et al., 2021). Overall, 89% of participants indicated a preference to share any genetic susceptibility information on their own with their families, with 87% disagreeing with the idea of a doctor providing this information to their families (De et al., 2021). Further, a higher level of concern was discovered for participants with less knowledge about genetic AD risk, which included those responding, "Do not know" to the question "It is possible to have AD gene but no symptoms of AD" (De et al., 2021, p. 40.). In contrast, participants with a higher level of knowledge regarding ApoE genetics expressed a significantly low level of concern regarding their ApoE genetic risk disclosure (De et al., 2021).

In a study by De et al., (2021) researchers considered the possibility that higher knowledge scores obtained by participants could be a reflection of the effectiveness of study-related information provided prior to ApoE disclosures. Researchers mentioned the possibility that this additional ApoE knowledge, coupled with an increased level of support provided by genetic counseling, may have reduced any concerns participants had after their ApoE risk disclosure. This belief is supported by not only the current research findings, but also past research literature from 2004 and 2018, in which study-related information and genetic counseling were considered critical ethical proponents for disclosure of genetic information (De et al., 2021; Hietaranta-Luoma et al., 2018; Vähäkangas et al., 2004). As a result, researchers concluded that the genetic knowledge provided through written materials, lectures, and counseling during the disclosure process appeared to reduce participants concerns.

Expertise

Many years ago, experts predicted that the rapidly changing field of genetic testing and the human genome project would eventually require primary care providers to become more involved in genetic test administration, genetic counseling, and privacy protection (Andrews et al., 1994). As the field has evolved, the demand for genetic testing and disclosure has started to exceed the number of available genetic specialists. An integrated approach involving other healthcare professions as well as patients and family members may be needed. However, this integrated approach will require a significant increase in training and education in the area of genetics and medicine for all clinicians and treatment team members, not just those who specialize in genetics. In addition, there will continue to be an increased need for oversight

experts in healthcare, legislation, and ethics to ensure accurate genetic testing that minimizes risk and harm to patients (Andrews et al., 1994).

CHAPTER V: TECHNOLOGY USE IN APOE RISK DISCLOSURES

Direct-to-Consumer Genetic Testing Platforms and Related Studies

In August of 2011, direct-to-consumer (DTC) genetic testing was just starting to be offered to the public, with 28 companies providing testing within the United States (Kaufman et al., 2012). At that time, companies could provide genetic tests for 385 diseases and traits with the DTC company 23andMe providing services to at least 60,000 customers (Kaufman et al., 2012). One of the major challenges in genetic research has always been how to efficiently coordinate the gathering of human genetic data (Eriksson et al., 2010). In 2010, 23andMe partnered with research scientists to develop a new framework for addressing this challenge. Research scientists used this DTC company's customer base to administer web-based surveys for data comparison and analysis. This data was obtained using 13 surveys posted on the company website which was then filtered by inclusion and exclusion criteria for the researchers' study. Survey participants were also able to compare their responses to others upon completion of their own survey (Eriksson et al., 2010). Upon completion of this study, all involved recognized the time and cost influence this web-based framework could have on future genetic research with regards to fast and simultaneous recruitment for multiple studies (23andMe, 2010; Eriksson et al., 2010). The principal scientist at 23andMe articulated this approach further by stating, "Through 23andMe's web-based platform, the company can perform hundreds of studies in parallel. Our ability to contact individuals multiple times and ask follow-up questions puts us in a position to zero in on associations that could be the building blocks for future research aimed at prevention, better treatments, and potentially cures for a multitude of diseases and conditions" (23andMe, 2010, p. 1). During this study, 22 genetic traits were analyzed with over 9,000 pre-

existing genetic connections made while also making new genetic discoveries (23andMe, 2010). This research study confirmed the possibility of obtaining quality self-reported data from participants beyond traditional research methods. The traditional method of collecting data involves recruiting individuals with or without a particular trait or condition with these two groups then being correlated to locate single letter DNA differences connected to the trait or condition being studied. This newly discovered web-based framework allows for immediate recruitment for multiple studies simultaneously (23andMe, 2010). Further, the researchers for this study concluded that their state-of-the-art approach in collecting data over the Web would be a viable alternative for past participants who had provided DNA and received their genetic testing interpretations to obtain additional genetic information (Eriksson et al., 2010).

During this same year, utilizing genetic testing to understand AD was a growing health concern in America (23andMe, 2011). At this time, 5 million people were believed to have AD with that number to increase to 14 million by 2050. On this online platform, genetic information regarding AD was shared with the general public. The platform mentioned three additional AD gene variant findings from 2009 studies that had 35,000+ total participants and over 8,000+ participants with AD. These single nucleotide polymorphisms or SNPs (e.g., DNA building block) were found to have small effects on AD risk. It was surmised at this time by Dr. Nancy Pedersen at the Karolinska Institute in Sweden that AD appeared to be a polygenic and complex disorder (23andMe, 2011). For this reason, she recommended that doctors presently focus more on lifestyle changes with patients to reduce AD risk (23andMe, 2010b). A year later in 2012, the same online platform again shared AD genetic information about a new rare genetic variant associated with lowering the odds of AD by five times – A673T (23andMe, 2012). The rare

variant was only believed to be found in 1 of 10,000 people. At that time, this DTC company was offering its customers AD risk reports for both the ApoE variant and this new variant (23andMe, 2012).

In 2014, a year-long AD related study was conducted through this same DTC company from its online platform (Roberts et al., 2014). The study was conducted from 2012-2013, involved 1,004 customers who they surveyed at baseline, 1 month, and 6 months to determine impact of AD genetic risk disclosure. Research findings revealed that 70% of participants were very interested in their AD risk at baseline. There were 13% of participants who never unlocked their AD risk results at all. When comparisons were done between pre-disclosure and post-disclosure, no difference in depression and anxiety were revealed. Methods of assessing these variable were not specified. There was some small elevation in test-specific distress for both ApoE-ε4 positive and ApoE-ε4 negative allele participants, as well as a significant increase in their perceived AD risk after baseline (Roberts et al., 2014). ApoE-ε4 positive participants were significantly more likely to engage in healthier behaviors (e.g., supplements or insurance). The researchers concluded that this study only reiterated the public's growing interest in genetic testing for AD risk (Roberts et al., 2014).

In 2016, the National Institutes of Health (NIH) provided 23andMe with a grant in the amount of $1.7 million dollars aimed at creating an African American DNA sequencing panel to be used for more diverse genetic research studies in the future (23andMe, 2016). At that time, it was estimated that over 90 percent of genetic research had involved individuals of European ancestry. This initiative at the time involved the company's existing 1 million consumers, "including tens of thousands" of existing African American customers (e.g., website reported

45,000 African Americans participating in research in April/May 2016) and provided de-identified genetic data for use to by health providers worldwide (23andMe, 2016, p. 2). The company again planned to share this information through their online platform to assist in reducing the disparities in genetic research. Overall, the online platform was noted to be large and ethnically diverse enough to possibly affect change in this area.

One year later in 2017, it was announced that DNA tests for Alzheimer's risk were approved to be purchased in the U.S. (Hamzelou, 2017). It was further emphasized that the bulk of supporting DTC genetic evidence was focused on disease development, which was also the FDA's primary basis for approval. To get approved, DTC companies were required to demonstrate 99% gene identification accuracy and participant recommended communication with a healthcare professional or genetic counselor pre-disclosure (Hamzelou, 2017). The FDA also required that DTC companies provide consumers with ample opportunities to opt out of AD genetic risk testing any point during this process, which was not the case for some DTC companies five years earlier (Friedlander, 2018).

In 2018, the discrepancy between the FDA's strict requirements for DTC companies was voiced as an issue of inconsistency and confusion for consumers (23andMe, 2018). In response, the FDA issued a consumer safety warning regarding all non-approved DTC tests by listing them on their website (23andMe, 2018).

Several years later in 2021, a DTC company collaborated with Medscape and surveyed 1,000 primary care physicians about their attitude on DTC genetic health testing (23andMe, 2021). This data was compared with a similar survey completed in 2018. The data revealed that current PCPs are now twice as comfortable explaining the pros and cons of genetic testing and

discussing and interpreting genetic results. In addition, 80% of PCPs are likely to suggest DTC genetic testing for patient health reasons with 61% of PCPs requiring FDA oversight to recommend a genetic test. Further, 71% of PCPs are now open to making referrals to genetic specialists versus only 44% in 2018. The PCPs also indicated they are now four times more comfortable ordering genetic testing (46%) and two times more comfortable making treatment decisions using genetic test results (41%). The conclusions reached were that an improved PCP genetic testing outlook was due to the increased utility and impact on patient care (23andMe, 2021).

Benefits versus Risks

The debate regarding disclosing gene testing results to the public has been longstanding (NIH, 2010). Similar to genetic risk disclosure, DTC genetic testing has also been surrounded in controversy (Bloss et al., 2012). For example, in 2012 when 23andMe received a U.S. patent for their approach in determining disease risk for Parkinson's, the research community responded with tension and skepticism (Allyse, 2013). Prior to this event, a negative history with genetic research existed where individuals and groups objected to their genetic information being used without their knowledge and for someone else. One example occurred at Miami Children's Hospital at their research institute when parents of children with Canavan's Disease legally sued the institute when the facility used tissue samples to research the etiology of Canavan's disease and patented the results for future profit. Allyse (2013) posited that the public is typically very supportive of medical progress, with their trust at the center of biomedical research. Therefore, participants need to know the researchers they are working with are fair and honest with their genetic data. Unfortunately, to reduce the cost of research, the direct-to-consumer environment

has been compelled to obtain participants consent simultaneously with disclosure, leaving no participant opportunity for an informed refusal (Allyse, 2013). This lack of conversation can ultimately result in misunderstanding and negative feelings. During this recent patent incident with, it seemed clear to researchers that additional attentiveness and communication is necessary to ensure a clear understanding regarding any additional use of data samples (Allyse, 2013).

Further conflict arose in 2011 when the government provided investigational information on four companies providing DTC genetic testing (Bloss et al., 2012). Their investigation revealed a conflict between the DNA predictions and participants' medical histories. Their investigation included 3,416 individuals who purchased DTC genomic tests. A review of the conditions researched revealed that 5 of the 15 provided risk estimates were based primarily on self-reports pertaining to health history (Bloss et al., 2012).

In 2012, after several genetic research conflicts, researchers decided it was necessary to track and analyze the exact level of public understanding and awareness of DTC genetic testing to assist in modifications to DTC services (Finney Rutten et al., 2012). They wanted to determine the extent of public interest in DTC genetic services to help policymakers assess if consumer concerns were confined to a subgroup or more widespread within the general population. The data from National Trends Survey in 2008 was analyzed, including an N = 7,674 participants and again in 2011 with an N = 3,959 participants. The data points reviewed included socio-demographics, health care, internet use, and population density. The researchers discovered an increase in DTC awareness from 29% (2008) to 37% (2011), which was considered significant. The participants with increased awareness included 50-74 year-olds, college graduates, individuals with a healthcare source, individuals with a prior cancer diagnosis,

internet users, and those living in urban environments. The researchers emphasized the importance of continued public awareness monitoring, along with analysis in the use of and response to DTC genetic risk information. The researchers concluded that such continued analysis could help maximize benefits and minimize the risks of DTC genetic testing and inform public health (Finney Rutten et al., 2012).

In 2013, a DTC genetic testing study using online surveys sought to address the concerns that this method of disclosure may cause an increase in anxiety and a decrease in healthy behaviors (Egglestone et al., 2013). They noted three common concerns for DTC genetic testing: limits in clinical validity of disease connections reported, differences in assessments provided, and the unknown significance of small changes. Researchers provided an online survey to 275 participants who had (n = 189) or had not (n = 86) received their test results. The surveys revealed that 27.3% of all participants reported a change in health behaviors, and 24.6% reported a change in health anxiety with 85.3% of all participants indicating a reduction in anxiety. The participants who had received their risk disclosure reported significantly better health behaviors than those who had not yet received their genetic testing status. Researchers concluded that the data demonstrated some association between DTC genetic test results and increased healthy behaviors. They noted that this was one of only two studies performed with DTC genetic testing regarding the possible benefits of risk disclosure (Egglestone et al., 2013).

In 2014, survey results indicated that 91% of Americans understood that their genetic information is an important part of their health (23andMe, 2014). At that time, 82% of Americans appeared to understand the connection between their genetic testing and their risk of disease, with 77% knowing genetic conditions or diseases can be passed on to their children.

However, the specifics of genetic science were much less well understood by the public, as 41% did not know that DNA is organized into chromosomes, only 24% had the understanding that they have 23 pairs of chromosomes, and a small 10% understanding that humans share >99% of DNA with all other humans. In this regard, the DTC company's Director of Business development indicated, "people have the opportunity to explore their own DNA – to more tangibly understand how their DNA may inform their health. As genetics becomes a more routine tool in managing health, it will be important for individuals to have a clear understanding of what genetics can tell them – and what it can't" (23andMe, 2014, p. 2). During this same time period 23andMe partnered with Pathway Genomics in a longitudinal study to analyze psychosocial, behavioral, and health outcomes in regards to DTC genetic testing (Carere et al., 2014). The study utilized web-based surveys administered three separate times involving 1,464 participants with 71% completing follow-up surveys, 64% completing all surveys, and 90% agreeing to being contacted for future research. The participants were 15.7% non-white and from a diverse range of education, income, and health categories. The researchers concluded that this online platform minimized costs while maximizing data integrity within a secure structure for research partners to transfer data. The researchers concluded that this web-based method of data collection, especially when participant driven, was a model demonstrating successful genetic testing industry engagement along with academic autonomy. These conclusions were based on data reflecting high participant completion and response rates with confirmed access for future inquiry and research (Carere et al., 2014).

In 2015, researchers took a closer look at the consumer impact of DTC genetic testing without using a health care intermediary (Boeldt et al., 2015). This controversy is focused on the

behavioral and psychological effects DTC genetic testing may have on the consumer. Notable is the fact that the FDA recently became involved in this debate by issuing a warning letter to DTC company, 23andMe questioning the safety of the delivery of genetic risk data. During this time, the FDA instructed them to discontinue their marketing of health-related tests. In response, the company suspended their return of health genetic risk estimate to customers until FDA concerns were addressed. This 2015 study looked at whether or not consumer differences influence psychological and behavior outcomes after DTC genetic testing (Boeldt et al., 2015). These researchers explored consumers' most feared diseases and their responses after DTC genetic testing. Researchers analyzed data from Scripps Genomic Health Initiative (SGHI) a longitudinal study analyzing the psychological and behavioral impact of DTC genetic testing (Bloss et al., 2012). Participants had purchased a genetic test where web-based health assessments were completed pre-disclosure of genetic results and again at 3 months and 1year post-disclosure (Boeldt et al., 2015). The researchers for this study analyzed the data from baseline and 23 months post-disclosure.

During the 3-month follow-up assessment, participants were asked to identify the condition they were most concerned about and provide additional responses specific to this condition by completing the seriousness subscale of the Health Belief Model scale (Hochbaum et al., 1950; Boeldt et al., 2015). Other assessments used to measure outcomes included the Spielberger State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983), the Impact of Event Scale-Revised (IES-R; Weiss et al., 1996), the Block Fat Screener (Block et al., 2000), and the Godin Leisure-Time Exercise Questionnaire (Godin et al., 1985). Participants were also asked to reveal if they shared their results with their doctor (Boeldt et al., 2015).

There were 2,037 participants who completed the 3-month assessments (Boeldt et al., 2015). The results revealed that heart attack and Alzheimer's disease were the most feared conditions among these participants, with women fearing AD more and men fearing heart attack more. This analysis also indicated participants' level of distress regarding DTC genetic testing was not clinically significant, even when the perceived fear of a condition was high. Further, a perception of a higher level of control regarding disease development was associated with lower distress even when presented with the genetic risk for that disease. Research results revealed that higher perceived seriousness was correlated with higher levels of anxiety and distress (e.g., but not clinically significant levels), while the higher perceived control was correlated with lower distress levels. Researchers surmised that higher levels of perceived disease control could be a protective factor, and that higher perceived seriousness could cause more sensitivity in response to genetic risk results. They ultimately recommended that these disease perceptions be used to improve future genomic counseling, along with disease education and prevention methods (Boeldt et al., 2015).

The public's awareness of DTC genetic testing was also analyzed again in 2015, examining awareness levels, resources for testing, and psychosocial factors related to awareness within the U.S. (Agurs-Collins et al., 2015). The data for this analysis was obtained from the U.S. Health Information National Trends Survey of 2013 (HINTS; National Cancer Institute, 2011). Several social and cognitive variables were analyzed for level of DTC awareness. There were 3,185 participants analyzed (Agurs-Collins et al., 2015). The data revealed that 35.6% of participants were aware of DTC genetic tests, with most learning about them through the radio, television or and internet. The variables found to be most correlated with increased awareness at

the time of this study were participants with higher incomes (e.g., ≥$ 100,000), participants currently seeking cancer information, participants currently using the internet, and participants with higher numeracy skills (Agurs-Collins et al., 2015).

In 2017, 23andMe conducted another national survey regarding the public's interest in DNA testing (23andMe, 2017). They marketed to the public on their website so it is participant driven through the online platform. Existing customers (many of whom were initially ancestry customers) complete the survey and DNA studies they want to complete. The results provide some new and contrasting information, including the fact that 74% of individuals were interested in genetic testing, despite 75% of participants not knowing humans consist of 23 chromosomes. Of those surveyed less than 8% had participated in at-home DNA testing with one of the barriers being the cost. Only 17% of participants indicated that privacy was a reason they were not seeking testing with the DTC company. Of those customers completing this survey, 80% acknowledged security concerns about DNA data protection. Regarding those concerned, 88% of participants admitted not knowing or understanding the precautions DNA testing companies take to secure electronic information. Most of the participants, 4 out of 5, were willing to test if their data could be used to fuel research for more cures or treatments. Finally, an overwhelming 94% of participants reported feeling they have a right to at-home DNA testing (23andMe, 2017). Additional survey results also confirmed this information and noted that although the public did not fully consider the potential risks of DTC genetic testing, they did generally perceive it as useful information in managing their health (Roberts et al., 2017).

In 2018, the importance of confirming raw data results obtained from DTC genetic tests was emphasized by a smaller study involving 49 raw data samples (Tandy-Connor et al., 2018).

The researchers who analyzed this data mentioned the importance of accuracy and quality control in DTC genetic testing. They noted that some DTC companies provide only the raw genotype data to their customers if it is requested. Further, this raw data may contain other variants, typically referred to as "incidental/secondary findings" by the American College of Medical Genetics and Genomics (Tandy-Connor et al., 2018, p. 1515). The researchers' purpose in this study was to analyze existing DTC raw data within their genetic testing database for consistency and accuracy. To this end, they queried their internal database for the testing sample used, which was previously identified for DTC genetic testing from January 2014 to December 2016 (n = 49). A total of 26 unique variants were submitted for testing, along with 4 variants located deep within the analytical range of most labs. Participates were primarily female (91.8%), 30-49 years old (53.1%), and Caucasian (51.1%) with seven individuals having a personal history of disease, whereas 35 participants had no reported history of disease reported. The majority (40.8%) who ordered confirmatory testing were medical geneticists or counselors, in addition to oncologists (20.4%). A single-site analysis was ordered for 44.9% of cases and a single-gene or multi-gene panel was ordered for 55.1% of the cases with most orders (87.8%) testing for cancer genes. During their analysis they discovered that 40% of variants in a variety of the DTC raw data genes were false positives. Some of this DTC genetic test raw data had been designated as "increased risk" or classified as benign at other labs. The researchers during this study emphasized the importance of confirming DTC raw data variants with a clinical lab (Tandy-Connor et al., 2018).

Current State of Direct-to-Consumer Genetic Testing and Disclosure

In 2021, researchers sought to explore the use of DTC online recruitment registries to quantify the enrollees' characteristics and ApoE genetic testing within the DTC environment (Ryan et al., 2021). The method used was that of an online survey involving enrollees at the University of California Irvine Consent-to-Contact (UCI C2C) Registry. All C2C enrollees that were 50 years old or older were invited to participate. The study had no exclusion criteria. Prior to the survey, participants were required to either watch a 5-minute video about DTC genetic testing, AD and ApoE or read an educational pamphlet pertaining to the same topics. The online survey was administered after the video or pamphlet review with this subsequent data managed through Research Electronic Data Captured (REDcap; Ryan et al., 2021). During this survey, researchers questioned whether not participants knew their ApoE status before completing the survey and if so, how were they made aware. Participants were also asked about their level of interest regarding ApoE status and their willingness to share this information on their profile registry to be used for future research recruitment. Researchers also asked why if participants indicated limited or no interest one of these areas. Researchers received N = 1,312 valid responses for analysis, which equated to a 57% response rate that equated to 64% female and 89% white participant group. There were 77% of participants who were aware of DTC genetic testing, but only 7% had used it to discover their ApoE status. However, 81% of participants who did not know their ApoE status were interested in learning this information. In fact most DTC participants (97%) were willing to included their ApoE status in their registry profiles, with 92% of these participants open to being matched in additional studies. The 10% of participants who were unwilling to share their ApoE status on their registry profile, with half mentioning

their concern about insurance implications. One third of these participants also mentioned their feeling that their genotype was a privacy matter (Ryan et al., 2021).

During this study, researchers concluded that DTC use of enrollment registries may be an effective approach to help improve AD prevention trial recruitment in the future. They also noted the need for additional research to provide more insight regarding DTC results sharing and the validity of self-reported DTC data (Ryan et al., 2021).

In 2023, public survey information obtained explored the perceptions of physicians regarding several different areas of DTC (23andMe, 2023). This survey information came from a Medscape platform and was completed by 1,000 U.S. primary care physicians in October 2022. These physician participants had practiced medicine an average of 19 years with 90% of them practicing in the areas of family or internal medicine. Physician participants were invited to respond to the online survey, which was done in follow-up to surveys done in 2018 and 2020 regarding the same topic and on the same platform. This survey indicated that 92% of doctors in the U.S. who completed the survey (n = 925) believe genetic information is an important part of a patient's entire health profile (23andMe, 2023). Further, results from this study discovered that 66% of the doctors surveyed also believe that genetic testing could lead to improved outcomes for patients. Another online survey, conducted by a global insights firm Material+, also occurred in October of 2022, involving 1,501 Americans ages 18 or older. This survey revealed that 75% of survey participants would be more inclined to follow the advice from their doctors if their genetic profile was being used during DTC genetic testing.

In conclusion, since 2011 there have been increasing concerns regarding the expected number of individuals diagnosed with AD, currently and in the future, with the current 5 million

estimated to climb 35% to 14 million by 2050 (23andMe, 2010). In the past, researchers have confirmed the positive cost influence, increased efficiency, and increased participation and simultaneous recruitment advantages of DTC genetic research when compared with the traditional research approach (23andMe, 2010; Eriksson et al., 2010; Allyse et al., 2013). However, the ethical dilemmas surrounding privacy, confidentiality, beneficence, and non-maleficence have remained a concern debated within both genetic research and the general public (23andMe, 2017; Roberts et al., 2017). Despite these conflicts, repeated public surveys and online research studies have revealed that a significant portion of both the public and physicians who have completed these surveys are supportive and interested in both genetic testing and at home access through the DTC genetic testing online platform (Finnley Rutten et al., 2012; Roberts et al., 2014; Agurs-Collins et al., 2015; 23andMe, 2017; Roberts et al., 2017; and 23andMe, 2023).

CHAPTER VI: DISCUSSION

Summary of Literature Review - Conclusions

One of the most significant healthcare challenges of this century are Alzheimer's disease (AD) and mild cognitive impairment (MCI) with an estimated 40 million people currently suffering from these conditions (Alzheimer's Association [AA], 2020a). In fact, AD and MCI are expected to continue doubling annually until 2050. AD is considered to be a degenerative brain disease caused by complex brain changes, causing cell damage (AA, 2020a). MCI exists in between the expected decline of normal aging and a more serious decline of dementia (Mayo Clinic, 2023). Currently, we have limited knowledge as to the etiology or healing treatments for either AD or MCI (Roberts et al., 2014). Regarding AD, disease risk genes have been identified which increase one's likelihood of AD onset (AA, 2020b). In 2010, the Apo lipoprotein E (ApoE) gene was identified as one of these risk genes for AD (AA, 2020b). The ApoE gene has three allele versions: ε2, ε3, and ε4, with the ApoE-ε4 risk gene most strongly impacting AD onset at 40%-65% of those AD-diagnosed having this gene (AA, 2020b). MCI was initially introduced in 1982 and refined more in 2004 as a description for when one's cognitive skills are no longer normal but their daily functioning is still good (Reisberg et al., 2008; Petersen, 2004). This MCI term was further re-defined a year later to include different forms of MCI – amnestic, multimodal, and non-amnestic (Petersen and Morris, 2005). A significant correlation discovered between MCI and AD has prompted research studies regarding AD genetic markers in MCI patients, such as the ApoE genetic risk biomarker (Janoutová et al., 2015). In fact, the greatest success with prevention therapies for AD may occur very early in the disease process, most likely during the preclinical AD stage or with MCI patients (Sperling et al., 2014).

The additional disease risk biomarker for AD and MCI have resulted in an ethical dilemma regarding disclosure of the ApoE genetic risk factor to AD and MCI individuals. Previously, many health care providers were not willing to disclosure the ApoE risk factor to patients for fear of added harm (Green et al., 2009). In fact, there were times in 2011 and 2018 that the American College of Medical Genetics and National Society of Genetic Counselors even recommended against ApoE genetic testing of patients citing limited clinical benefit in: clarifying risk, improving diagnosis or prognosis, or informing treatment (Goldman et al., 2011). This debate about whether or not to disclose ApoE genetic risk factors to individuals, finds its ethical center in the ideals of autonomy, beneficence, and non-maleficence (APA, 2017). In order to further understand the issue, this literature review was done asking:

- Is ApoE genetic risk disclosure ethical, and what outcomes does it potentially generate for those at risk for AD, MCI patients, and preclinical AD patients?

My review of the literature on this topic revealed several significant findings. First with regard to autonomy and one's right to know, Kristman & Krieger argued that a patient's test results are part of their medical records and should be disclosed so that their health decisions can be informed and truly autonomous not stemming from some level of coercion or manipulation (2008). Informed consent can only be truly informed when an individual is provided with all the information. Further, autonomy applies to all individuals, not just those who report no history of anxiety, depression, or other mental health issues. Overall, the ApoE disclosure literature reviewed revealed that providing more information to participants typically resulted in positive outcomes, such as decreased distress, increased adherence to treatment, and more motivation to engage in healthy behaviors (LaRusse et al., 2005; Ashida et al., 2010; Roberts et al., 2014). The

means and methods of communication in genetic testing information, and genetic counseling have also played a significant role in outcomes.

All healthcare providers need more training and education in human genetics disclosure, including psychologists. Psychologists are likely to be faced with many of these individuals both before and after receiving genetic test results, including their ApoE genotype. For this reason, Psychologists need to be genetically literate and prepared to provide ethical and effective treatment to these individuals when they are processing this information (Guttmacher, 2001; Richmond-Rakerd, 2013). Psychologists must also protect their clients right to autonomy when deciding to consent to genetic testing. The genetic counseling process is meant to provide individuals with enough information so they can make a fully informed decision (Richmond-Rakerd, 2013). A psychologist with strong viewpoints misaligned with their client, could negatively impact client autonomy and the client-counselor relationship.

In the cases of individuals struggling with anxiety and depression, psychologists may need to provide psychoeducation on the potential for exacerbation of symptoms after receiving genetic testing results, and a treatment plan to address any post-disclosure symptomatology. However, this psychoeducation and treatment plans should be ethically limited to objective information, as the means and methods of communication could directly affect an individual's outcomes. The variations in communication or preferred coping methods should be considered by psychologists during this process (Khan et al., 2015). Psychologists' awareness of how their values can influence this process are embedded within the APA ethical principles, specifically principles D and E (APA, 2017). The clients' wants and needs should exist absent of any influence from the psychologist (Richmond-Rakerd, 2013).

In regards to autonomy and privacy rights, both HIPPA and GINA have attempted to create a balance, between one's rights and societal interests (Clayton et al., 2019). This balance remains focused in the areas of attaining both open sharing that increases scientific knowledge within society and the protection of an individual's right to privacy (National Library of Medicine, 2021). The literature reviewed concluded that this issue should be interpreted on a case-by-case basis while considering a social justice view to perceive all the ethical dimensions of this issue (Morrisey & Walker, 2018).

Direct-to-consumer (DTC) genetic testing also effects individuals' autonomy, in that their privacy, confidentiality, and self-determination needs protection. Overall, at this time DTC genetic testing research revealed that more structure and control need to be implemented to protect individuals' genetic information, including surname use, information sharing and use of genetic information in future research (23andMe, 2017; Allyse, 2013; Gymrek et al., 2013; Roberts et al., 2017; Ryan et al., 2021). Further, continued monitoring of the publics' awareness regarding the specifics of genetic testing results (e.g., ApoE results and meaning) remains a necessity when maintaining autonomy (Ryan et al., 2021).

The second ethical ideal of beneficence explores the risks and benefits (e.g., clinical utility) of genetic testing in an effort of trying to help individuals by placing their welfare before all else (APA, 2017). The literature reviewed explored if ApoE genetic disclosure led to improved health outcomes for ApoE positive individuals, as well as the risks that occurred due to ApoE disclosure (Burke, 2014). Clinical research trials served as the best resource for this literature review of outcomes. However, as AD research continues to progress, additional biomarkers that detect disease, especially for individuals with MCI, may prove invaluable in the

future (Caprioglio et al., 2022). The use of technology and DTC genetic testing has also provided researchers with the capability to gather significant amounts of information from those participating in genetic testing (Prince & Berkman, 2018). This method of research has the benefit of providing unlimited information and the potential to modify how risks and benefits are view in genetic testing (Prince & Berkman, 2018).

The significant findings within this ApoE disclosure literature review included studies surrounding long-term care insurance, positive behavioral impacts, overall adopting of health and lifestyle improvement habits, increased adherence to treatment plans, and access to supportive resources (Zick et al., 2005; Chao et al., 2008; Heritaranta et al., 2014; Roberts et al., 2014; Arias et al., 2021). The only negative health behavior discovered was some participants taking excessive amounts of vitamin E after their ApoE disclosure (Bemelmans et al., 2016).

In 2005, researchers discovered a tendency of ApoE positive participants to purchase long-term care insurance, a positive post-disclosure outcome with the potential to benefit both the participants and their families (Zick et al., 2005). A further study regarding long-term care insurance also revealed the need for more comprehensive federal and state regulations pertaining to such insurance coverage for genetic risk participants, especially since AD typically requires extensive long-term care treatment (Arias et al., 2021). Researchers also discovered that ApoE risk disclosure had the potential to generate additional motivation for participants to engage in improved health and lifestyle behaviors and increased treatment compliance (Chao et al., 2008; Hietaranta-Luoma et al., 2014).

The third and final ethical ideal of non-maleficence (e.g., do no harm) was also explored throughout the ApoE disclosure literature. Overall, the significant findings within the literature

included studies surrounding the psychosocial impacts of ApoE disclosure on individuals, the exposure to discriminatory treatment post-disclosure, and direct to consumer disclosure negative outcomes. The literature analyzing psychosocial impacts regarding ApoE genetic risk disclosure revealed minimal negative psychological impact on participants. The literature revealed that psychological distress in response to predictive testing is mild and transient (Crozier et al., 2015; Heshka et al., 2008). In 2019, Roberts et al., surmised that these findings suggest that psychological harm from genetic testing, even for fatal conditions, is typically less than initially feared. The REVEAL literature from 2005 indicated the same or a lower level of anxiety post ApoE genetic risk disclosure with any distress reported as unrelated to genetic testing (Roberts et al., 2005). Another 2005 study expanded this further by discovering that participants distress was lower the more genetic risk and AD information they were provided with (LaRusse et al., 2005). In fact, the literature from 2009 discovered communication of one's ApoE results to someone else actually had a positive impact on the ApoE carrier (Ashida et al., 2009; 2010). It should be noted that a few studies reviewed did reveal slight increases in distress post ApoE disclosure, but nothing at a clinically significant level or prolonged, with most related to testing distress and not ApoE disclosure (Burke et al., 2010; Boeldt et al., 2015; Bemelmans et al., 2016).

As far as discriminatory treatment regarding ApoE genetic testing and post disclosure, insurance companies have been known to refuse to pay for the testing, mentioning its limited clinical benefit (Arias et al., 2021). This literature review did not find any occurrences of ApoE post disclosure long-term care exclusionary practices by insurance companies. However, with 40 million individuals currently suffering with AD and MCI and an expected annual doubling of

that number until 2050, the potential for discriminatory practices by insurance companies is an area of notable concern (AA, 2020a). Ethical practices of non-maleficence by healthcare providers and psychologists should include educating individuals about the importance of long-term care insurance coverage prior to genetic testing or even biomarker testing for AD.

Further, to prevent doing harm to ApoE genetic testing individuals, the literature emphasized the immediate need for psychologists and other health professionals to have specific ethical guidelines in human genetics (Richmond-Rakerd, 2013). Psychologists are currently following their own APA ethical code of conduct which is not tailored to genetic risk counseling for AD, dementia, or MCI (Richmond-Rakerd, 2013). In fact, the U.S. has had a dementia plan for early detection and accuracy since 2020, but there are still no genetic counseling guidelines for psychologist or other healthcare professionals (Richmond-Rakerd, 2013). The National Dementia Plan for the U.S. also listed a failure to disclose a risk status diagnosis (e.g., ApoE, MCI) as a gap in the guidelines (Richmond-Rakerd, 2013). This gap is definitely doing harm to those at risk for AD in the United States. The current approach involves MCI individuals being provided with prevention options and limits, information on the uncertainty of an AD diagnosis, genetic counseling suggestions, and long-term planning possibilities. In an effort to assist psychologists and healthcare providers, several best practices for genetic testing communication regarding AD and MCI participants within the U.S. have been created within the research literature (Roberts et al., 2020). Currently, U.S. guideline for MCI individuals recommend that preclinical disclosures and genetic counseling be performed in-person with both the individual and a family member present (Alpinar-Sencan & Schicktanz, 2020).

Finally, psychologists and other health professionals are in need of additional training in order to provide genetic counseling services for MCI and AD individuals both pre and post ApoE disclosure. A large part of the ability to do no harm to others as clinicians stems from competency and training. Psychologists practicing both within and outside medical settings, along with psychologists working in genetic research, education and policy, have an immediate need for this specific genetic counseling training. Uncertain and complex information such as ApoE risk disclosure, MCI and AD diagnoses, are influenced by an individual's expectations, emotions, and biases which then effect their thoughts, communication, and decisions (Khan et al., 2015). Psychologists and other health professionals need specific training in genetic counseling so that they can determine their client's level of genetic literacy, information preference, view of providers and perception of current health (Khan et al., 2015). Psychologists and other health professionals must also be able to identify their own biases in this area and understand how to minimize their influence during the genetic counseling process (Richmond-Rakerd, 2013).

Limitations of Literature Review

This literature review was limited in that much of the current research stems from the REVEAL study or its participants and datasets, which were initially done in 2005 and continued in 2009 and 2010. Some additional research beyond that dataset was able to be integrated. Since 2019, the focus appears to be shifting away from the REVEAL database to focus on pre-clinical risk disclosures for possible disease prevention similar to past BRCA genetic testing research for breast cancer.

Another area of limitation involved the fact that a majority of the studies until 2019 contained exclusion criteria for participants with pre-existing, clinically significant depression, anxiety, or other psychological conditions. Due to these exclusions, these earlier studies are not generalizable to the general population. A research study that includes individuals with mild anxiety and depression would provide a clearer picture as to how ApoE disclosures could affect someone that is more sensitive to distress.

Further, the lack of diversity regarding race and socioeconomic status within the literature may have skewed participant samples and study outcomes, and further reduces generalizability. The use of traditional in-person genetic disclosure and counseling models for most of the literature could limit the generalizability for other methods, such as DTC genetic disclosure and testing. The over reliance on certain depression and anxiety scales throughout the literature as primary outcome measures may have also limited this review.

Recommendations for Further Research

Future research should further explore pre-clinical disclosures, direct-to-consumer disclosures, and genetic counseling to ensure that the ethical standards of autonomy, non-maleficence, and beneficence are adhered to moving forward. Specifically, a randomized study with non-clinical participants ages (60-75) outside of the REVEAL studies, that utilizes a DTC platform approved by the FDA for recruitment of participants and the ability to obtain a more diverse group of participants or another sampling model's design to obtain more diverse participants, without any exclusions for conditions such as anxiety and depression is recommended. The baseline and subsequent assessment appointments should be face-to-face either in-person or through Zoom (recorded) with a trained clinician who can provide adequate

genetic disclosure and genetic counseling. Post-disclosure assessments would occur at 1 week, 1 month, 6 months, and 1 year. Long-term care insurance would need to be confirmed prior to any participation in this study.

Initial intake paperwork would be completed through the online platform for screening prior to baseline assessment appointment. At baseline assessment appointment, participant's intake information would be reviewed for any additional information. The assessments utilized during this study could include: 1) Montreal Cognitive Assessment (MOCA; Nasreddine et al., 2005; a cognitive measure which can be administered in 10-12 minutes and has been found to have 80.48 % sensitivity and 81.19% specificity in the detection of MCI in patients over 60 years of age when compared to the MMSE at 66.34% sensitivity and 72.94% specificity; Ciesielska et al., 2016), 2) Patient Health Questionnaire (PHQ-SADS; Spitzer et al., 1994; a depression, anxiety, and somatic measure which can be administered in 15-20 minutes and has been found to have good internal consistency, test-retest reliability, convergent, construct criterion, procedural and factorial validity regarding anxiety, high internal reliability and construct validity regarding somatic problems, and was highly consistent regarding depression) This assessment also provide clinicians with severity cutoff points of 5, 10, and 15 (e.g., mild, moderate, and severe) to assist in differential diagnosis, and 3) Impact Event Scale Revised (IES-R; Weiss & Marmar, 1996), a distress measure that can be used with both healthy and frail older adults, can be repeatedly administered to monitor progress, with a hyperarousal and intrusion subscales and good predictive validity regarding trauma correlating well with the DSM-IV criteria for PTSD. The test is best used for recent trauma events (e.g., genetic risk disclosure; Christianson & Marren, 2012).

MOCA raw scores below 26 are considered impaired with MCI individuals averaging 22.1 and individuals with AD averaging 16.2 (Rosenzweig, 2020). Therefore, only participants obtaining a MOCA raw score of 26 or greater would be included in the study. These cognitive normal participants would continue to complete the additional assessment measures. Only individuals with "severe" levels of pre-existing depression or anxiety on the PHQ-SADS would be further excluded. Participants not excluded would be scheduled for their follow-up appointments. These follow-up appointments would be conducted either face-to-face in person or online through Zoom. Participants would then provide their DNA sample to the DTC company for analysis of the ApoE genetic risk factor. A risk disclosure appointment would be scheduled immediately, along with the follow-up appointments at 1 week, 1 month, 6 months and 1 year.

Considering the information obtained from past ApoE risk disclosure literature, both quantitative and qualitative, additional qualitative research questions would be asked to further clarify the participant's understanding of the ApoE genetic risk factor, mild cognitive impairment, and Alzheimer's disease during the baseline interview and follow up appointments could include:

- What is your understanding of the ApoE genetic risk factor?
- What is your understanding of mild cognitive impairment?
- What is your understanding of Alzheimer's disease?
- What questions do you have about this genetic test?
- What is your biggest worry about this process now?
- What is your biggest need right now?

- Who is your main support in this process?
- Would you like your support person to be present during and after the disclosure appointment?
- What are your current stressors?

Upon completion of this initial pre-clinical study pertaining ApoE risk disclosure and participant outcomes, subsequent studies could involve analysis of pre-clinical participants ages 60-75, and a closer analysis of any changes to their health behaviors and lifestyle patterns after ApoE risk disclosure. A similar design would be used in these studies as well.

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