THE EFFECTS OF ULTRASOUND ON QUALITY OF LIFE: AN EXPLORATION OF ULTRASOUND AS A DIAGNOSTIC AND TREATMENT MODALITY FOR NEURODEGENERATIVE DISEASES

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ABSTRACT

The Effects of Ultrasound on Quality of Life: An Exploration of Ultrasound as a Diagnostic and Treatment Modality for Neurodegenerative Diseases

Doctor of Medical and Health Humanities Dissertation by

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Neurodegenerative diseases, such as Alzheimer's Disease (AD), Parkinson's Disease (PD), and Amyotrophic Lateral Sclerosis (ALS), pose a significant impact on individuals and caregivers globally. Late-stage diagnosis and the absence of cures contribute to emotional anguish and the loss of independence and autonomy. Traditional diagnostic methods often confirm these diseases only after irremediable degeneration has begun, which can lead to a considerable decline in a patient’s quality of life. This dissertation aims to address these challenges with a proactive approach to advocate for the integration and implementation of ultrasound in neurodegenerative diagnostics and treatment interventions. Leveraged advancements in vascular functionality research, predominantly in cardiovascular and cerebrovascular scopes, provide an opportunity of possibility for early detection and treatment. Focused ultrasound arises as a key element to augmented drug delivery and neuromodulation without subsequent damage to adjacent regions. The integration of ultrasound techniques holds significant potential for neurodegenerative disease management, that offers optimism around earlier diagnostics and treatment interventions with improved quality of life and economic feasibility for patients and their caregivers.

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INTRODUCTION

Neurodegenerative diseases pose a significant public health risk and economic burden to many people worldwide. These diseases can wreak havoc for both patients and caregivers as the time spent post-diagnosis can invoke unsettled emotions due to the typical late-stage diagnosis and lack of cure. The onset of physical and cognitive symptoms quickly consumes the lives of those affected and leaves them with an absence of independence they once had over their daily lives.

Some of the most common neurodegenerative diseases that affect patients and families are known as AD, PD, and ALS. These types of neurodegenerative diseases currently have no known cure and tend to be diagnosed once the onset of symptoms have started. Many clinicians are only able to confirm a diagnosis of these diseases once physical or cognitive degeneration has begun, as the signs and symptoms of physical and cognitive decline present with attributes that can be indicative of a neurodegenerative disease. Clinicians have ways to confirm a diagnosis through tests and other biomarker measures, however, the most concrete way to confirm a diagnosis has typically been performed through post-mortem assessment.

Researchers have been able to identify ways to confirm a pathology prior to death. However, sometimes these established protocols are only able to identify the disease pathology once symptoms have significantly progressed. This poses a major peril to quality of life for both patients and caregivers that are burdened by these diseases because more progressed and severe cases of AD, PD, and ALS ultimately deplete individuals of their ability to exercise independence and freedom over the autonomy of their own body,

restrained by the physical and cognitive hinderances of these diseases, which directly affects how they may value and view the quality of their own life.

Quality of life remains a significant attribute to the role of human existence and tends to be one of the foundational principles that many individuals use as a basis for their life blueprint. The way in which humans take on daily tasks within their lives can typically be centered around in what they find value and how the quality of those experiences influences their entire view of life. When individuals are stripped of their independence and autonomy over their body and life due to a disease that cripples their ability to complete daily tasks that were once performed without conscious effort, the life blueprint they once created becomes seemingly unattainable. This helpless fight for survival becomes their sole purpose for being.

The initiatives set forth in this dissertation aim to address barriers to early diagnosis and treatment of AD, PD, and ALS with a solution driven incentive to overcome these obstacles with the potential implementation and complimentary accent of ultrasound in neurodegenerative diagnostics and treatment interventions. The advancements in current research centered around vascular functionality and the relative association to physical and cognitive degeneration found as a result of neurodegenerative diseases poses a significant contribution to the future of neurodegenerative disease diagnostics, as many of these screening methods have already been established as successful tools in the cardiovascular and cerebrovascular space.

The addition of research in the area of focused ultrasound has also offered paralleled importance to the potential treatment approaches for neurodegenerative diseases due to the increased effectiveness in drug delivery and the variability in beam

intensity manipulation to alter the functionality of anatomical structures and associated cellular systems without subsequent damage of adjacent tissue.

The purpose of this dissertation aims to shed light on the current research for the diagnosis and treatment of neurodegenerative diseases through the successive addressment on how these approaches can be complemented or modified with ultrasound focused methods to obtain optimal patient centric outcomes relative to quality of life and economic sustainability.

PART ONE

Early Diagnosis

Transcranial Doppler Ultrasound (TCD):

Transcranial doppler ultrasound is a form of imaging used to assess varying functionality of the brain. This method of imaging has been used to evaluate cerebral hemodynamics, a common indicator of cognitive impairment, which can be associated with the early onset or potential development of neurodegenerative diseases (Roher, et al. 2011). Transcranial doppler ultrasound advancements have allowed for more thorough identification of vascular flow, anatomical structures, and associated recognition of biomarkers due to the hyperechogenic response of increased sound waves that present in varied shades during ultrasound imaging (Baldacci, et al. 2020). As a result, there is now potential to utilize TCD as an early diagnostic tool for neurodegenerative diseases, which can help clinicians identify a pathology prior to the progression or onset of symptoms (Roher, et al. 2011).

These improvements have made TCD an optimal tool in point of care ultrasound for emergent and resource-limited settings (Valaikiene, et al. 2022 & Allen, et al. 2023). The importance of TCD as a form of POCUS can not only be understood from the early diagnostic capabilities, but value also remains in the quality-of-life benefits for patients. This form of bedside imaging is noninvasive, inexpensive, and does not emit radiation (Valkaikiene, et al. 2022). These factors become imperative as ultrasound technology advances because the technology brings a quality of life focus back to patient care. Medical device advancements like imaging systems are often highly expensive and tend to emit radiation to the patient. This does not mean that those imaging modalities do not

yield a positive result that ultimately outweighs the negative effects, but simply demonstrates that there may be room for more improved diagnostic techniques, such as ultrasound, that can reduce the cumulative expenditure on a patient's quality of life.

Although TCD, as a form of point of care ultrasound, may be viewed as uncommon or even precocious at current for the early diagnosis of neurodegenerative diseases, there are studies that confirm cerebral hemodynamics or vascular functionality in the brain and increased density of sound waves during imaging referred to as hyperechogenicity, may be a starting point to incorporate this form of point of care ultrasound imaging more readily (Roher, et al. 2011 & Baldacci, et al. 2020). Echogenicity can be defined as the way in which the sound waves from the ultrasound "echo" or bounce back between structures with different densities and material make up (Waller and Maibach, et al. 2005). The hyperechogenic response can be understood as one way these echoes reverb against various structures.

TCD as a diagnostic tool can be viewed as uncommon because there are limited studies that address the appropriate parameters during image acquisition, which contribute to the diagnostic accuracy of neurodegenerative diseases (Allen, et al. 2023). Lack of research publications on TCD parameters during image acquisition results in limited standardization of imaging protocols, which can directly affect an accurate and confirmed pathology (IBID). Therefore, the consideration of TCD as an early diagnostic tool for neurodegenerative diseases must reflect more recent publications around cerebral hemodynamics and hyperechogenicity to help determine a pathology and the identification of biomarkers. Additionally, current uses of TCD and the associated outcomes should also be considered.

The analysis and identification of these current practices and successful outcomes, can further support the potential use of TCD not only as an effective diagnostic modality for neurodegenerative diseases, but also as a way to increase quality of life during a patient's disease process, as will be explained in Part 4.

Current Uses:

TCD physics and fundamentals are based off the Doppler Effect, which takes place when ultrasound waves emitted from the Doppler probe are transmitted through the skull and reflected by the movement of red blood cells through the intracerebral vessels (Purkayastha and Sorond, 2012). The difference between the emitted and reflected waves directly correlates to the speed of the moving red blood cells, which determines the velocity of blood flow through the vascular structures, ultimately providing insight into the various potential indications of disease or complications (IBID). Bone density of the skull and ultrasound beam frequency play a critical role in the functionality of TCD because there are specific acoustic windows found through thinner regions of bone that help to obtain optimal image quality (IBID). Intracranial blood flow relative to the associated anatomical structures are critical to understand as part of the TCD image acquisition process (IBID).

TCD has more commonly been used as a diagnostic tool to assess cerebral hemodynamics for the determination of intracranial stenosis, which can be understood as the the narrowing of blood vessels in the brain; detection of emboli also known as blood clots; vasospasms in subarachnoid hemorrhaging, which reduces blood flow; status of cerebral autoregulation; acute ischemic stroke; midline shift; increased intracranial pressure; peripheral nerve lesions; and intracranial masses (Allen, et al. 2023 &

Valaikiene, et al. 2022). Many of these focus points have a direct relationship with adjacent vascular structures that can influence such events. The acknowledgement of this relationship remains important in the consideration of TCD as an early diagnostic tool for neurodegenerative diseases. For example, cases that involve intracranial masses demonstrate this relationship as there are typically vascular structures associated with the blood supply of those masses, which can be measured through the use of TCD.

The four main acoustic windows that are utilized can be referred to as, the transtemporal window, the transorbital window, the submandibular window, and the suboccipital window (Purkayastha and Sorond, 2012). Although specific windows can provide insight for different arteries and indications, in most cerebral hemodynamic assessments a four-window evaluation that includes the course of blood flow within each major branch of the circle of Willis would provide the most ideal results (IBID). The circle of Willis aims to assist in anterior and posterior blood flow circulations through the brain, which allows for more efficient blood flow functionality throughout (Rosner, et al. 2018).

Variation and shifts in the velocity during TCD assessment are critical fundamental attributes of TCD to understand because those indications provide insight into the various disease states and conditions correlated with changes in vascular flow (Purkayastha and Sorond, 2012). This also indicates that the diagnosis of any disease that does not have a direct correlation with blood flow in the brain may not be a plausible candidate for TCD. The association of cerebral hemodynamics and cognitive impairment, a common characteristic of neurodegenerative diseases such as AD, PD, and ALS, make

a valuable tool as an early diagnostic assessment for such disease states (Roher, et al. 2011).

The echogenic effect that can occur between various structures during TCD assessments provides valuable insight towards the factor identification of different neurodegenerative pathologies (Ihnatsenka, et al. 2010). Echogenic effects are when ultrasound waves reflect off nearby tissue or other anatomical structures, which can generate variations in image representation on ultrasound systems displays (IBID). Echogenic effects can be identified as either hyperechogenic (white on the screen), hypoechogenic (gray on the screen), or anechoic (black on the screen) (IBID). The fundamental characteristics of ultrasound wave reactions like density and composition of various structures are an important component in the justification of TCD as a diagnostic tool for neurodegenerative diseases. For example, many of the biomarkers that have been found to be indicative of a neurodegenerative pathology contain cellular components that can alter the reflective response from the ultrasound waves on adjacent tissues or anatomical structures, which has been shown to be evident in the substantia nigra of PD patients most likely due to increased iron and gliosis levels (Surguchov, A. 2022).

Modulation of motor movement and function of the reward system pathway are some of the associated mechanisms of the substantia nigra (Sonne, et al. 2022). The findings exemplified in research of the susbstantia nigra can help investigators determine how these associations may be able to provide confirmation of a disease pathology (Surguchov, A. 2022). Additionally, echogenicity can present in other pathological assessments, which adds to the well-rounded and justifiable approach.

Further analysis and evaluation of current TCD research can influence use cases between many specialties of medicine, which can allow for wider adoption across clinical practices. More specifically, the area of neurology may find value of TCD to help identify neurodegenerative pathology. Avid researchers have even touched upon how this diagnostic form has been seen to be superior to MRI in visualizing deep brain structures through high image resolution (Walter, 2011). TCD benefits have shown to be non-invasive, inexpensive, bed accessible, and emit a zero-radiation footprint, which can help to provide a better quality of life and standard for patients.

TCD for Neurodegenerative Disease Diagnostics

The current uses of transcranial ultrasound can help determine applications for the identification of neurodegenerative disease indications. Successes related to cerebral hemodynamic assessment are important to understand as these outcomes are most relatable to the functionality of TCD. Pattern recognition and collective observations through the functionality of vascular structures provide insight on the characteristics of the structures themselves. Cardiovascular health stands as an important indicator in identification of illness and disease.

Office visits to a primary care physician for a check-up typically begin with the assessment of vitals like blood pressure, pulse ox, and heart rate. These simple tests can begin to open the door for further interpretation on where the examiner needs to go to identify the cause of current symptoms. Similarly seen with TCD, examiners have been able to assess the vascular state within the brain to determine if there are blockages, poor velocity, and even potential masses that may be impeding on optimal health (Roher, et al. 2011). The accumulation of TCD research has allowed researchers to make connections

between cerebral hemodynamics and the neurodegenerative disease pathologies like AD, PD, and ALS, although this has not been fully explored (IBID). In order to understand how cerebral hemodynamics could be assessed as a possible indicator of neurodegenerative disease through the use of TCD, one must be familiar with the succeses of other use cases relative to complications, disease states, and pathologies.

Vinciguerra and colleagues have set the precedent of an associated link between cerebral hemodynamics and cognitive impairment. Findings from previous studies have assessed how TCD can be utilized to determine the relationship between cerebral hemodynamics and brain lesions associated with small vessel disease and cognitive impairment (Vinciguerra, et al. 2019). Vinciguerra and others found specific measures of cerebral perfusion and vascular resistance were significantly associated with white matter lesions and patients with vascular cognitive impairment and no dementia (VCI-ND) (IBID). The characteristics of VCI-ND individuals did not present with substantial functional impairment, but still exhibited signs of cognitive impairment associated with some variation of cerebrovascular disease (IBID). Cerebral hemodynamic fluctuations observed through TCD, warrant the push for further exploration on how cerebral hemodynamic fluctuation may present differently amongst various neurodegenerative diseases like AD, PD, and ALS.

Alzheimer's Disease and TCD:

Associated research related to cerebral hemodynamics and AD has been thoroughly studied by Roher and colleagues. This study has proposed that AD may be a systemic degenerative disease linked to age-related deterioration of cardiovascular functions (Roher, et al. 2011). Although this area has not been fully explored or

understood, the conclusions that have been drawn to link progression and the onset of AD with cardiovascular state and functionality remains promising. Current research statistically links atherosclerotic vascular disease with AD through indirect biomarkers of atherosclerotic vascular disease, like the build-up of blood cholesterol, serum lipid profile, and C-reactive protein, however this form of correlated testing may not be as accurate as TCD in identifying the pathology of AD (IBID).

Research that supports the use of transcranial ultrasound in the identification of vascular functionality and abnormalities, leads to more cohesive discussion on how the relevance of these indications may contribute to a confirmed pathology prior to the onset of symptoms for patients with AD. This knowledge can further advance the adoption of this technology to help treat potential AD patients prior to or at the onset of symptoms to reduce the potential severity and slow the progression of the disease.

Research has found that cerebral arteries are often morphologically altered and dysfunctional in AD (Roher, et al. 2011). One study found that there was an increase in severity of atherosclerotic stenosis of the cerebral arteries in AD confirmed subjects compared to age-matched non-demented control subjects (IBID). This observation and conclusion drawn by Roher and colleagues demonstrates that the underlying dysfunctionality of the cerebral arteries in confirmed AD patients can be associated with an increase in atherosclerotic stenoses, which directly impacts blood flow, and therefore oxygen and nutrients to the brain, resulting in decreased cognitive function (IBID). The velocity of blood flow and identification of stenosis can be visualized through TCD, which can then potentially be used as an initial determinant of the AD pathology for patients exhibiting cognitive decline. The unanswered question as to whether a confirmed

AD diagnosis could be made in patients not exhibiting cognitive decline, may be answered through the use of biomarker identification with TCD, which will be discussed in later sections.

Calcification within the arteries can increase vascular rigidity and resistance commonly seen in a diminished circle of Willis and leptomeningeal artery assessment with TCD (Roher, et al. 2011). Cerebral arterial and capillary resistance can be common in AD patients due to amyloid-β (Aβ) peptide build up within the vascular wall (Roher, et al. 2011). The build-up of the Aβ protein can increase cellular toxicity and affect blood flow, which can even lead to an increased risk for cerebral hemorrhages and neuronal injury (IBID). The association of these two observations can be potentially linked together in the AD pathology with the confirmation and presence of the Aβ biomarker in conjunction to stenosis of the cerebral arteries.

The study by Roher, et al. found there was a linked association between hemodynamic and structural alterations of the cerebral arteries in potential AD diagnosis, which allows one to insinuate that decreased cerebral blood flow, increased arterial rigidity, decreased arterial compliance, and recognized myocardial impairment are systemically linked to dementia and cognitive decline (Roher, et al. 2011). A more recent study supports these discoveries with the recognition of cerebral blood flow as the main delivery system for oxygen and glucose to the brain (Graff, et al. 2023).

When oxygen and glucose to the brain decrease, the risk for cognitive impairment and decline increases. Cerebral blood flow has been shown to decrease with age and seen to be depleted two times greater in regions associated with AD (Graff, et al. 2023). One can infer that as a result, disposition and functionality of the cerebral blood flow can

serve as a possible indicator of the AD pathology (IBID). Additionally, AD exacerbates the loss of cerebral blood flow ten times greater annually compared to healthy aging individuals, which further supports this correlation (IBID). A common trend in this data links cerebral function to cognitive decline in AD patients, which can potentially be identified and monitored with TCD. Studies support this argument with the verification of cerebral blood flow activity on TCD screenings.

The lack of current data on cerebral blood for an AD brain compared to that of a healthy aged individual, could most likely be due to the fact that diagnostic modalities such as TCD, have not been thoroughly explored as a confirmation method for the AD pathology (Graff, et al. 2023). If one takes the data confirmed from a vascular diagnostic perspective exemplified in Roher and colleagues and correlates that to a more recent connection between cerebral blood flow and AD seen in studies performed by Graff and associates, a trend arises relative to the functionality of blood flow and the associated AD pathology (Graff, et al. 2023 & Roher, et al. 2011). Graff, et al. confirms that the decrease in cerebral blood flow significantly increases with the onset of AD, while Roher, et al. confirms that the pulsatility index measurements and mean velocity flow of specific arteries were found to be significantly different between both the non-demented control group and the AD group (IBID). This demonstrates that the functionality of cerebral blood flow and analysis of cerebral hemodynamics can provide further insight into the pathology of AD in patients exhibiting cognitive impairment or decline (IBID).

A strong argument can be made about the relationship of cerebral hemodynamics and the AD pathology, which further supports the use of TCD as an assessment tool for identification of cerebral hemodynamic factors. These cerebral hemodynamic factors can

potentially help aid in the diagnosis of AD patients prior to the onset of symptoms or increase in disease progression.

Parkinson's Disease and TCD:

PD can commonly be classified by indications of dopaminergic neuron degeneration in the mesencephalic location of the substantia nigra with Lewy body inclusions also understood as disaggregated proteins associated with the disease (Brisson, et al. 2021). Current research focuses on the clinical indications which include two common phenotypes, classical which presents with tremor as the main manifestation (TD), and akinetic-rigid type (AR) (IBID). However, researchers have found that vascular lesions have become an incidental finding of this pathology (IBID). The principal association found between vascular functionality and PD remains under investigation due to limited knowledge and presence of these associations in a confirmed case diagnosis (IBID). Researchers have also identified that magnetic resonance imaging does not appear to be an essential tool for the confirmation of PD, however, white matter lesions associated with PD on MRI images, have been found to be linked to root comorbidities such as, hypertension and diabetes, which are associated with cerebral vascular dysfunction (Brisson, et al. 2023).

The exploration of AD and cerebral hemodynamics can allow researchers to elaborate on TCD discoveries that support this theme and associate them with root cardiovascular comorbidities identified and incidentally found amongst confirmed PD patients to draw conclusions on the potential benefits of cerebral hemodynamic assessment with the use of TCD for the confirmation of a PD diagnosis. PD has less data in terms of identifiable intracellular biomarkers and indicators compared to AD, so the

conclusions that must be drawn should be resourced and correlated with several comparable studies.

Brisson and colleagues have provided more recent research on the vascular associations with PD, which include a study that utilized transcranial color-coded sonography (TCCS), a form of transcranial doppler sonography, to assess the cerebral hemodynamics of PD patients in either the TD or AR group (Brisson, et al. 2023). These groups were then further divided into two subgroups with individuals that had either two or more cerebrovascular disease risk factors or the other group that had no more than one (IBID). As similarly seen in the cerebral hemodynamic analysis of AD patients, blood flow velocity, pulsatility index, resistance index, and middle cerebral artery at a rest state were analyzed (IBID). The difference in the TD versus AR phenotype may result in varied vascular functionality, which implies that effective identification of this disease pathology must consider other indicators aside from what was studied by Brisson and colleagues.

Brisson and colleagues showed that 66.7% of PD patients with the AR phenotype presented with a cerebrovascular reactivity impairment, while the TD group presented with less at 37.5% (Brisson, et al. 2023). Furthermore, the PD patients that had two or more vascular risk factors presented cerebral hemodynamic data that was indicative of vascular brain pathology (IBID). This confirms that cerebrovascular function in PD patients can play an integral role in the identification and diagnosis of the disease pathology. This can also potentially signify that the silent damage of cerebrovascular vessels can theoretically lead to the worsening of PD symptoms if these indications are not identified early in the disease process. Comparable to this TCCS study, another

smaller study by the same group assessed individuals with the same variable phenotypes and found altered cerebrovascular reactivity in the TCD results, which confirms that the presence of root cerebrovascular disease is commonly associated with PD patients regardless of the phenotype (IBID). This delineation highlights the importance of the fundamental ultrasound technology given that TCD in either form, traditional or TCCS, can show cerebrovascular functionality in the assessment of PD patients.

There are different identifiable factors that can contribute to cerebrovascular functionality. One study looked at iron deposition in the location of the globus pallidus and found that PD patients with the AR phenotype presented with more iron accumulation than that of PD patients with the TD phenotype (Brisson, et al. 2023). The overload of iron in the brain tissue has been found to be increased in patients with cerebrovascular disease, which supports the argument that cerebral hemodynamic assessment in PD patients would be worth exploring to identify the onset of disease more quickly (IBID). The presence of iron and the association to cerebrovascular disease and PD provides importance relative to echogenic responses (Ma, et al. 2022). The representation of echogenic responses with TCD, can present in cases of PD as hyperechogenicity, which has been shown to be associated with the substantia nigra, present in approximately 70-90% of PD patients (IBID). Ma and colleagues reference another study that looked at hyperechogenicity of the substantia nigra post-mortem and found there to be increased levels of iron, which has been shown to be associated with dopamine synthesis (IBID). Iron plays a critical role in electron transport and ATP production, which makes it an essential nutrient for brain function (Foley, et al. 2022). This in turn supports the research of Ma and colleagues, which identified how potential

overload of iron ions and poor metabolism of iron can affect motor function (Ma, et al. 2022).

Additionally, this can possibly be correlated to the depleted motor function in PD patients (IBID). The collective knowledge central to the crucial role iron plays in dopamine synthesis and how poor metabolism of iron can potentially affect motor function in PD patients, allows one to associate the hyperechogenicity seen in the substantia nigra of dopaminergic neurons to the possible overabundance of iron in the vessels of the substantia nigra and adjacent regions (Brisson, et al. 2021; Foley, et al. 2022; Ma, et al. 2022). The value of this correlation could allow for a potential confirmation of the PD pathology through the use of TCD (IBID).

Ma and colleagues reference another study that identifies TCD of the substantia nigra as the "gold standard" for PD, where the image results presented with a 92.9% positive predictive value and 88.3% accuracy (Ma, et al. 2022). This indicates that the echogenic response of the substantia nigra seen with TCD presented with a sensitivity and specificity that met the standard or threshold for a positive PD indication compared to other potential diagnoses. This increased reaction and sensitivity as referenced above, could be related to the increase of iron deposition seen in the presence of poor iron metabolic processes. The reason for poor metabolism of iron can potentially be related to a broken redox cycling where the ferrous ion (Fe^{2+}) which becomes oxidized to form the ferric ion (Fe^{3+}), to facilitate in the catalysis of repeated chemical reactions at low iron concentration levels, does not function properly (Foley, et al. 2022). These thresholds of sensitivity and specificity seen with TCD are identified for various diseases and disease

states, which help to establish a standard that clinicians can use to delineate fluctuations in pathological characteristics of disease.

One form of TCD assessment requires visualization through the temporal window of the skull, however, sole focus of this window in TCD assessment can create limitations relative to habitus disposition (Ma, et al. 2022). Additionally, this can result in a variability of indications, which some researchers argue does not make TCD a plausible tool for PD diagnosis (IBID). However, even with these oppositions, most researchers have found that hyperechogenicity of the substantia nigra was seen to be common in PD patients, which can be confirmed with multiple studies (Ma, et al. 2022; Todd, et al. 2023; Brisson, et al. 2021). Researchers that have provided more in-depth insight related to iron overload and poor iron metabolism seen in PD patients, strengthens the argument that the hyperchogenicity seen in the substantia nigra of TCD assessment can be a credible focus point in the early diagnosis and pathology identification of PD.

Amyotrophic Lateral Sclerosis and TCD:

ALS can be classified as a progressive motor neuron disease, where very little available information and knowledge associated to the etiology and exact pathology has been established (Sennfalt, et al. 2023). The current research and data supports that there are biomarker indicators of the disease and some modalities relative to image acquisition, however, a 10–16-month diagnostic delay impedes on the possibility for a confirmed diagnosis (Vidovic, et al. 2023). Additionally, much of that time crosses over into the 2–4-year survival rate (IBID). Accurate, reliable, and quick diagnostic techniques must continue to be explored to help optimize time that remains for ALS patients from the onset of symptoms to the end of life. Previous discussions of this analysis have shown

that underlying cardiovascular comorbidities have been linked and correlated to the onset and progression of neurodegenerative diseases like AD and PD. The use of TCD has been explored as a plausible diagnostic imaging modality in an attempt to assess and identify these disease pathologies earlier on in the disease process. ALS specifically, presents with even less available information on how the use of TCD can be utilized to identify this pathology because there has been minimal growth in this area of research for the last decade (Goutman, et al. 2022). The analysis of multiple studies should be reviewed to delineate potential associations and conclusions on how TCD can be implemented into the identification of the ALS disease pathology.

Previously observed PD studies outlined cerebrovascular disease presented as a common risk factor, this can also be seen in ALS with evidence that supports pathological alterations of small cerebral blood vessels in ALS individuals (Brisson, et al. 2023 & Schreiber, et al. 2023). Identification of impaired vascular brain health has been shown to have detrimental effects on motor neurons through lowered vascular endothelial growth factor levels commonly seen in ALS patients (IBID). Additionally, studies have shown that the vascular endothelial growth factor can be mutated in ALS patients, which has been comprehended through the scientific exploration of ALS rodent models and patients (IBID). The association of microvascular cells, such as endothelial cells, are important to understand given that research of transgenic ALS mice have shown that these cells become active in the asymptomatic and preclinical disease stages (IBID). Drawn from this evidence, one can conclude that if cerebrovascular disease analyzed with TCD can attest to alterations in endothelial cell levels, there may be further exploration that can be done to identify the pathology of ALS prior to the onset of

symptoms in patients predisposed, at risk, or already have presented with signs of cardiovascular disease and root cardiovascular comorbidities.

This means that if the results in ALS mouse models can be translated to results seen in TCD assessment in humans, this data may provide insight into the preliminary pathology of ALS, and thus aid in earlier confirmed diagnoses. Theories and information understood about vascular brain health must be considered as this hypothesis has not necessarily been tested in current research.

Additionally, research supports that the vascular brain health may be potentially mediated through vascular patterns of blood supply to the motor cortex, which supports the claim that decreased motor function and cognitive decline are seen as symptoms in sporadic ALS patients (Schreiber, et al. 2023). The article by Roher and colleagues focused on AD and the assessment of vascular rigidity and resistance in the circle of Willis, which similarly correlates to what Schreiber and cohorts identify, that shows more than two thirds of the population exhibit structural variations in the anatomical configuration of the circle of Willis (Roher, et al. 2011 & Schreiber, et al. 2023). This is turn can lead to variations in vascular supply to the brain (IBID).

Conjoined within the circle of Willis are various arteries that transport blood to different regions of the brain which include motor areas and cognitive areas like the motor cortex and hippocampal arteries (Schreiber, et al. 2023). The anterior cerebral artery supplies downstream blood to the vessels in the medial motor cortex, while the medial cerebral artery supplies blood through the vessels connecting into the lateral motor cortex (IBID). Vascular blood supply can be compromised when individuals exhibit cerebrovascular disease, which can essentially impact effective cognitive and

motor function (IBID). If vascular endothelial cells are mutated or do not function properly, there could potentially be alterations to the small cerebral blood vessels, which would further support the claim that causal vascular dysfunctionality may in fact contribute to the ALS pathology. Based upon this information one can infer that research in support of TCD for the identification of anatomical arterial characteristics and disposition in cerebrovascular disease and other vascular related anomalies may help lead researchers to more effective ways to identify the ALS pathology. The addition of ALS biomarkers and other indications in conjunction to what has been understood in the TCD assessment for cerebrovascular disease may help aid in an earlier confirmed diagnosis even before the onset or progression of symptoms. If this theoretical assessment of TCD could be seen as effective, the future of how ALS can be initially identified and studied in practice could be highly impactful.

The discussion of hyperechogenicity has been present in many sources relative to neurodegenerative diseases, but more specifically with PD. The hyperechogenicity of the substantia nigra visualized with the use of TCD, has been a common observation by researchers (Ma, et al. 2022). This can be seen in about 70-90% of PD patients (IBID). A noteworthy connection seen between ALS and PD, can be seen in one study which showed in 70% of the assessed ALS patients where transcranial sonography was used, hyperechogenicities were found at the substantia nigra (Prell, et al. 2014). This study also confirmed that 47.9% of ALS subjects showed clear hyperechogenicity of the midbrain structure, which remains part of the brainstem (IBID). The control group, which consisted of 78.3% of subjects did not show hyperechogenicity within the brainstem

(IBID). This shows that ALS patients demonstrated significant changes in the hyperechogenicity of the brainstem compared to the control group (IBID).

The study by Prell, et al. was published in 2014, which can be considered dated compared to research at current, however, since there has not been much advancement in research for ALS within the past decade this observation seems logical. There have been released studies within the last year or two for PD research, where parallel observations have been identified in PD patients, such as Ma, et al. which can then be reflected for ALS patients in studies such as Prell, et al. This shows that although modest research has been published for ALS and TCD as of recent, the commonalities seen from a hyperechogenic perspective in PD and a vascular health perspective in AD, may warrant further investigation for the ALS pathology (Brisson, et al. 2023; Ma, et al. 2022; Roher, et al. 2011; Schreiber, et al. 2023).

Current TCD and ALS research shows that vascular brain health can potentially impact motor function and cognitive decline in ALS; hyperechogenicity has been observed in the substantia nigra in patients with ALS; the phrenic nerve may be indicative of ALS as this has been potentially identified as the first nerve damaged within the disease progression and confirmed through the use of ultrasound (Schreiber, et al. 2023; Ma, et al. 2022; Laucius, et al. 2023). The systematic review and analysis of multiple studies are dichotomized to propose how TCD, or other transcranial ultrasound approaches may be valuable for the identification of ALS pathology earlier on in the disease progression or before the onset of symptoms. The analysis of ways in which TCD can be utilized currently to identify some of the pathological indicators of AD and PD, can help exemplify the common overlap with ALS, which helps to support the argument

that the same diagnostic properties could be utilized for and earlier diagnosis of the ALS pathology. The established overlap relative to AD and vascular brain health, which may be similarly seen with ALS patients, in conjunction to the observations of hyperechogenicity in the substantia nigra for both PD patients and ALS patients, could make the differentiation of these neurodegenerative diseases difficult. This showcases why other potential indicators should be further explored, such as phrenic nerve degeneration.

A study performed by Laucius, et al. aimed to assess motor nerve size reduction of ALS patients to identify whether this technique would provide more indicative results that could lead to an earlier diagnosis of the pathology (Laucius, et al. 2023). This study hypothesized that the size of the phrenic nerve in an ultrasound assessment would be reduced in ALS patients (IBID). The phrenic nerve can aid in respiratory functionality and can be affected in ALS patients (IBID). Ultrasound of the phrenic nerve does not assess cranial vascular focus points, however, the use of this form of ultrasound as a secondary approach after the TCD analysis may be beneficial. The reason for this is because researchers found that the phrenic nerve was significantly smaller on both sides of the neck in ALS patients compared to those without the disease (IBID).

The phrenic nerve plays a crucial role in respiration, which can explain the reason this structure was being assessed as a potential initial indicator early on in the disease process (Laucius, et al. 2023). However, due to limited parameters of homogeneity and echogenicity in the ultrasound assessment of the phrenic nerve, in addition to the limited research studied on this topic, Laucius and colleagues expressed there should be more data to assume the position of this as an indicator for the early diagnosis of ALS (IBID).

If future studies can yield the same statistically significant results with more verification on ultrasound parameters, this as well as the vascular brain health and hyperechogenicity of the substantia nigra could become strong indicators of the ALS disease state, which can lead to an earlier diagnosis and intervention of treatment to potentially slow the progression of the disease.

Detection of Biomarkers

As previously outlined, many neurodegenerative diseases demonstrate a confirmed pathology from various biomarkers in post-mortem assessment (Baldacci, et al. 2020). The post-mortem assessments do not allow for early diagnosis or disease intervention as they are performed after death, which can thus limit a patient's quality of life in the preliminary disease process, onset, and throughout degradation. Researchers have focused on current biomarker assessment tools to address this issue, as they may provide a plausible solution in the analysis of neurodegenerative diseases prior to or at the onset of the disease process (IBID). This includes blood neurofilament light-chain analysis used to assess neurodegeneration associated with frontal and temporal lobe dementia, ultrasensitive assays, protein misfolding amplification assays, and ultrasound (IBID). The main focus of these potential assessment tools, which include ultrasound, would be to determine how they may be utilized for patients and their quality of life.

Ultrasound as a minimally invasive technique offers a cost effective, easily accessible, and zero-radiation footprint approach to diagnostic care. Biomarker assessment and practices post-mortem may provide insight into how they could be performed on patients that are alive with the use of ultrasound. This is a theoretical approach that must be further explored to determine if such thought could hold any

credibility. The loss of proteostasis and accumulation of misfolded and aggregated proteins currently present in the pathologies of AD, PD, an ALS must be addressed to further identify how these biomarkers may provide insight into the pathology of these neurodegenerative diseases (Baldacci, et al. 2020). Indications associated with vascular flow and echogenic response seen through the use of ultrasound should also be studied to determine how they may also be utilized as a preliminary measure to assess patients prior to or at the onset of the neurodegenerative disease process (IBID).

An analysis of the previously discussed use cases for TCD for vascular brain health, hyperechogenicity, and other forms of ultrasound assessment, such as phrenic nerve ultrasound for AD, PD, and ALS, should be analyzed against the current advancements of confirmed biomarker assessment tools to determine how these can impact a patient's quality of life and how ultrasound may be a potential option to address gaps in early diagnosis for AD, PD, and ALS.

Alzheimer's Disease:

Various studies have been performed post-mortem within the last decade to identify specific biomarkers of AD that include a wide range of sequenced genomes to determine variants indicative of early-onset and sporadic phenotypes of the disease (Baldacci, et. al 2020). Some of these variations in the disease assessment post-mortem presented with TDP-43 and α-syn depositions, however, the hallmarks of the AD pathology remain a focal point in the examination of this disease; neuritic plaques primarily containing Aβ42 peptide aggregates that contribute to the foundational build of proteins and neurofibrillary tangles comprised mostly of abnormal amounts of phosphorylated tau protein (3R/4R tau) (IBID). Baldacci and others explain how

cerebrospinal fluid with concentrations of Aβ42 in conjunction to hyperphosphorylated tau proteins are proxies of the AD pathophysiology (IBID). This means that plaques and tangles are hallmarks of the AD pathology and the presence of these hallmarks on a cellular level within the cerebrospinal fluid can aid in the confirmation of the AD pathology. Cerebrospinal fluid plays a critical role in the nourishment, waste removal, and protection of the brain and remains located in the ventricles of the brain and other spaces between the cranium and spine (Telano and Baker, 2023). The assessment of cerebrospinal fluid remains important due to the integration this fluid has within the brain.

Cerebral amyloid angiopathy is a cerebrovascular disorder where an accumulation of amyloid in the small to medium sized blood vessels has been shown to be present in autopsy studies for 85-95% of AD patients (Baldacci, et al. 2020). Relative to the TCD studies where cerebrovascular disease was confirmed, this outcome provides further support on the use of this assessment tool as a plausible solution in the identification of AD biomarkers earlier on in the disease process. The buildup of amyloid can lead to perivascular drainage impairment, which ultimately can lead to blockages and enlargement of the perivascular Virchow-Robin spaces, commonly associated with small vessel disease (IBID).

The confirmed diagnosis of cerebral amyloid angiopathy follows what can be referred to as the Boston criteria, which has recently been modified to help improve diagnostic accuracy in live patients (Baldacci, et al. 2020). A confirmed diagnosis of cerebral amyloid angiopathy can have indications that overlap with lobar cerebral microbleeds and ischemic lacunes, which provides reason for this shift (IBID). The

overlap of indications creates many diagnostic challenges for image modalities like magnetic resonance imaging (MRI) however, these confronts have improved with shifts in the diagnostic protocols overtime (IBID).

Many of these biomarkers are assessed post-mortem because there currently are no blood biomarkers specifically modified due to the AD pathology (Gonzalez-Ortiz, et al. 2023). Much of the present research focuses on confirmed biomarkers of the disease post-mortem and how they can be analyzed in vivo either through assays or imaging such as MRI, which makes this applied concept important to note. Minimal data exists that supports the confirmed pathology of this disease with these established biomarkers in vivo because many of these assessment tools are not equipped to differentiate biomarker variations and specifications of protein variants and constructs within the blood across various pathways (IBID). This suggests that certain biomarker indications may need to be isolated to subject specific components of the protein constructs in assays to further delineate an AD prognosis from other neurodegenerative diseases with overlap. A remarkable study done by Gonzalez-Ortiz and colleagues may have paved the way for identification of the tau biomarker in cerebrospinal fluid (IBID).

This study found that tau in the adult human brain can present with six isoforms between 352 and 441 amino acids long, but tau in the peripheral tissues, which includes the liver, heart, kidney, and pancreas, present with a higher molecular weight and the isoform exon 4a insert (Gonzalez-Ortiz, et al. 2023). Based upon what was identified from the tau protein interactions, researchers created an antibody assay to determine if the brain-derived tau proteins could be targeted in the blood separate from the peripheral tau associated protein constructs (IBID). Gonzalez-Ortiz and colleagues found that the brain-

derived tau measured in the serum/plasma did in fact pair with the cerebrospinal fluid samples targeted tau forms that originated in the brain, which denounces studies that claimed plasma total tau does not correlate with cerebrospinal fluid tau (IBID). This was confirmed in autopsy cases that showed brain-derived tau increased regardless of whether they presented with mixed pathologies (IBID).

Based upon the discoveries of AD and the associated biomarkers of plaques that contained Aβ42 peptide aggregates, tau tangles, and potential cerebral amyloid angiopathy, a common association or focus of research has been centralized around blood or the vascular system. The associations drawn around TCD and AD are supported with current research concentrated on identification of AD biomarkers because there are primary commonalities between protein and vascular functionality within the blood of the AD pathology. Ultrasound or TCD may pose as a plausible solution for the assessment of biomarker tests in vivo because they are easily accessible, emit a zero-radiation footprint, and are inexpensive. Studies have shown that TCD can help facilitate the identification of cerebrovascular disease and other vascular malfunctions or complications while the patient is alive and thus may help confirm a diagnosis for AD prior to disease progression based on the biomarker evaluation.

Research completed by Gonzalez-Ortiz and colleagues may have initiated a future focus for the identification of brain-derived tau within in the blood for further investigation on the behavioral interactions of these protein aggregates in the cerebral blood relative to a patient's physical symptoms (Gonzalez-Ortiz, et al. 2023). The physical symptoms are based on observations associated with physiological characteristics of cerebrovascular vessels (IBID). If clinicians can identify the presence of

brain-derived tau within the blood and analyze physiological behavior within the cerebrovascular structures, a confirmed diagnosis of AD may be possible prior to disease progression, which can then potentially aid in earlier treatment intervention and increase a patient's overall quality of life. This also then opens the door for further research within the pharmaceutical companies to not only find solutions that continue to slow the disease progression, but also help in the isolation of these specific biomarkers for precision treatment, to completely suppress the functionality of these disease complications within the body.

Parkinson's Disease:

PD presents with notable clinical symptoms that include, in some cases tremors, rigidity, and cognitive decline, where no reliable assessment method exists for PD, except for genetic tests of rare monogenic forms of the disease (Surguchov, A., 2022). Biomarkers that are currently studied for PD include, abnormal function of the presynaptic dopaminergic system, disease-associated α-synuclein (αSyn) aggregates, Amyloid-β (Aβ)/tau deposition, and low Aβ42 in cerebrospinal fluid (Baldacci, et al. 2020; Majbour, et al. 2022; Lim, et al. 2019).

Based on previous literature analysis, many researchers have confirmed that TCD visibility of the substantia nigra shows verification of dopaminergic activity with 86% and 96% accuracy amongst PD patients compared to controls (Baldacci, et al. 2020). Abnormal function of the presynaptic dopaminergic system or the preliminary release mechanism for the neurotransmitter dopamine, can be correlated to one potential component of early diagnosis identification; however, some researchers have stated that the neurodegenerative process begins many years before clinical symptoms arise, such as

an abnormal increase in the size of the substantia nigra (Majbour, et al. 2022). The identification of biomarkers are highly imperative to improve early diagnostic protocols so that clinicians can identify neurodegenerative shifts in either anatomical structures, cerebrovascular functionality, or misfolded protein structures prior to the onset of clinical symptom presentation.

The focus in recent years has been to identify diagnostic tools that aid in the early detection of synucleinopathies, one of which presents as the misfolded αSyn biomarker that aggregates in tissue and biological fluids found to be associated during the clinical stage of PD (Majbour, et al. 2022). Studies have shown that there are elevated levels of αSyn oligomers in cerebrospinal fluid in PD patients, which directly correlate to the motor function of PD patients (IBID). The detection of αSyn aggregates in cerebrospinal fluid has typically been performed either through antibody immunoassays such as ELISA, or assays that expose the self-propagation characteristic of αSyn aggregates like seed amplification assays (SAAs) (IBID). In short, this means that there are current ways to identify or measure αSyn aggregates within cerebrospinal fluid that can potentially confirm a diagnosis of PD or even provide insight towards the severity of the disease state, however, the performance of this research still remains in post-mortem assessment, which limits the amount of autopsy data available to researchers.

Due to limitations within biomarker research of PD, one must take the conclusions drawn from these various studies and piece together how they may be correlated and how this data may lead to more impactful ways of early pathology diagnostic protocols. αSyn aggregates have been found to be present within cerebrospinal

fluid of PD patients and cerebrospinal fluid flow dynamics are thought to be directly correlated to cerebral blood fluctuations (Majbour, et al. 2022 & Wang, et al. 2022).

This shows an overlap from a macro view perspective between anatomical systems and functionality. This all leads back to the brain through system movement such as vascular flow. Since most PD patients suffer from physical symptoms associated with dysfunction of these brain altered systems, one can conclude that they may in fact all be correlated. These conclusions between cerebrovascular functionality and physical symptoms of PD patients were evaluated in earlier sections; however, with the knowledge that αSyn aggregates can be identified in cerebrospinal fluid, and researchers have shown that cerebrospinal fluid flow can be correlated to cerebrovascular functionality, one could infer that the αSyn aggregates within the blood may present a distinguishable characteristic of cerebrovascular functionality compared to individuals not currently diagnoses with a neurodegenerative disease. This analysis and hypothesis would need to be confirmed through a more concrete study analysis, but the theoretical approach presents with hopeful probability.

The hypothesis made between αSyn aggregates in cerebrospinal fluid and cerebrovascular functionality, can also be made about Aβ or Aβ42 found in the cerebrospinal fluid of PD individuals. One can assume based upon the distinct way cerebrovascular flow presents in cases of PD, when confirmed amounts of Aβ42 are present in the cerebrospinal fluid, that the Aβ plays a significant role in the vascular functionality and flow. This would then mean that TCD as outlined before, may be a potential solution for the identification of the PD pathology earlier on.

Studies focused on cerebrospinal fluid biomarkers in PD have continuously found decreased levels of Aβ42 in PD patients with dopamine resistant gait disturbances (Lim, et al. 2019). This can potentially link Aβ deposition involvement in autopsy reports to both cognitive and locomotor dysfunctionality (IBID). Researchers have also confirmed high tau and phosphorylated tau levels in the cerebrospinal fluid of PD patients are indicative of motor progression (IBID). Research remains underway for Aβ from a neuronal perspective; however, current research has touched upon the potential role of Aβ in synaptic transmission and how the inhibition of Aβ can possibly lead to cell death (IBID).

Identification capabilities of Aβ42 in blood flow with the utilization of imaging modalities such as TCD, could potentially help clinicians determine an earlier diagnosis for PD patients, as well as lead researchers to understand more sufficiently the severity of the PD prognosis and how factors such as Aβ and tau can contribute to the progression of cognitive and physical symptoms.

Amyotrophic Lateral Sclerosis:

ALS biomarker research remains limited, but understood physical impairments such as lower motor neuron and upper motor neuron signs have led to more potential neuronal associated biomarkers (Vidovic, et al. 2023 & Goutman, et al. 2022). Some researchers believe that nerve changes and degradation happen before muscle changes (Lopez-Navarro, et al. 2021). The reason for this can potentially stem from the increased neurofilament light chain levels seen in the cerebrospinal fluid of ALS patients, which has been correlated to axonal damage, that resulted in the release of these neurofilaments into the blood and cerebrospinal fluid (Baldacci, et al. 2020). Neurofilaments are neuron-

specific cytoskeletal proteins that help to stabilize the axon terminals and can be categorized as light (NfL), medium (NfM), and heavy (NfH) (Gagliardi, et al. 2019).

Due to the high concentration of neurofilament found in the cerebrospinal fluid of ALS patients, researchers have probed this biomarker as hopeful for the future of ALS diagnosis and treatment (Gagliardi, et al. 2019). Identifiable factors found in the cerebrospinal fluid has helped researchers to distinguish neurodegenerative disease from other potential diagnoses (IBID). As previously discussed, research exists that supports the use of TCD to measure cerebrospinal fluid and the cerebral hemodynamics of that fluid within the brain (Vinciguerra, et al. 2019). Cerebral hemodynamic fluctuations can shift as a result of cerebrovascular damage seen in small vessel disease and other cerebrovascular associations (IBID).

ALS individuals have been shown to exhibit indications of increased NfL levels in the cerebrospinal fluid (Vinciguerra, et al. 2019). Cerebrospinal fluid acts as a protective mechanism for neuronal tissues and pathways, which also helps to excrete waste from the brain (IBID). Due to the increase of these NfL levels, one can assume that cerebral dynamic fluctuations may resemble that of a stagnated or resistant flow in TCD assessment compared to health individuals. Some researchers believe that the movement of solutes in cerebrospinal fluid travel through the glymphatic pathway, which rely on fluid movement of the perivascular space for successful excretion (IBID). This demonstrates how the potential biomarker of NfL could be evaluated with TCD, which would help to implement a more standardized approach for ALS diagnostic protocols (IBID). This theory, however, would need to be tested across multiple studies of ALS patients and healthy controls (IBID).

Cerebrospinal fluid with NfL showed tremendous diagnostic accuracy for the delineation between ALS patients and health controls (Baldacci, et al. 2020). Additionally, another study showed phosphorylated neurofilament heavy chain (pNfH) presented with even stronger diagnostic accuracy, which helped to differentiate ALS individuals from ALS mimics (IBID). This study was also able to correlate pNfH with the association of cerebrospinal fluid YKL-40, a biomarker associated with glial activation and neuroinflammation (IBID). The increased specificity of these biomarkers can help to further distinguish ALS disease from other neurodegenerative diseases with visible overlap of characteristics and might even be seen as the first detectable event of neurodegeneration in the ALS disease progression (Gagliardi, et al. 2019). The release of neurofilaments due to axonal damage can not only be found in cerebrospinal fluid, but also in blood (IBID). This data helps to further support the potential use of TCD for the detection of cerebral hemodynamic fluctuations early on in the disease process. If TCD can be utilized to determine fluctuations of cerebrospinal fluid or blood flow in the cerebrovascular space, clinicians can then perform immunoassays to determine the presence of neurofilaments, which may aid in the diagnose of ALS earlier on in the disease process.

Due to the limited knowledge relative to ALS biomarkers and the lack of visible indications early on in the disease process, clinicians may find it difficult to determine when and how TCD could be utilized in conjunction to immunoassays to test for the presence of neurofilaments in either the plasma or cerebrospinal fluid. The recognition of upper motor neuron or lower motor neuron limb impairment can often be the first indicator that some sort of neurodegenerative disease may be at play (Vidovic, et al.

2023). Symptoms of these impairments can include decreased tongue motility; an increase in jaw or palmonmental reflexes; increase in deep abdominal reflex; and even spastic muscle tone (IBID). However, based on previous studies the disease progression may already become advanced by that point, which could be why researchers have studied NfL assessment and tendencies, due to the argument that NfL accumulation may begin prior to physical symptoms (Gagliardi, et al. 2019).

If neuronal indications of the disease are not assessed prior to physical symptoms, TCD may still be a plausible diagnostic solution to confirm that the physical impairments of the bulbar, cervical, thoracic, or lumbar regions that are indicative of a neurodegenerative disease and more specifically ALS (Vidovic, et al. 2023). This could also help clinicians to further distinguish ALS from other neurological conditions that can affect these same regions (IBID). The process to utilize TCD at that specific point in the diagnostic assessment can still be a helpful tool to help clinicians work through the decision tree of diagnostic presentations. If TCD can be utilized to assess the cerebrovascular status of ALS patients in conjunction to other forms of ultrasound to test for muscle atrophy, this may help clinicians delineate ALS from other neurodegenerative diseases. Especially neurodegenerative diseases like ALS, that have limited confirmed biomarkers. This could essentially help initiate more accurate diagnoses earlier on, which may also increase a patient's overall quality of life.

PART TWO

Treatment Modalities

Focused Ultrasound:

Focused ultrasound (FUS) an emergent tool utilized to noninvasively create lesions or provide temporary modification to targeted brain tissue, with minimal effects on adjacent tissue from the transferred ultrasound energy (Baek, et al. 2022). The invasive example of this procedure would require one to drill into the patient's skull and physically create the lesion typically with a lead. This procedure can be categorized as stereotactic lesioning (Fishman & Frenkel, 2017). The goal of both noninvasive and invasive lesion creation would be to essentially produce permanent damage to the targeted tissue which may function as the cause of an individual's neurological disease or disorder (Giammalva, et al. 2021). Another procedure similarly performed to treat movement disorders, also referred to as deep brain stimulation (DBS), follows this invasive approach, however, the treatment typically does not result in ablation, but rather the manipulation of that specific region, controlled through a regulated implanted stimulation device (Fishman & Frenkel, 2017).

The DBS procedure can somewhat be debated in terms of intentional brain injury as the lead that used to emit stimulation essentially creates a lesion, which could therefore be viewed as injury to the tissue. Ultrasound waves are generally referred to as high frequency sound waves, which can only proliferate in a "non-empty" space or middling (IBID). Ultrasound waves are created and received by the transducer comprised of piezoelectric crystals that produce these beams when they become electrically charged (IBID). Ultrasound waves operate at a high frequency; however, high frequency focused

ultrasound waves are a different approach to ultrasound, which use a focused approach at a higher temperature (IBID). The delivery of these higher frequency FUS waves rely on speed and acoustic impedance to reach a desired target (IBID). Density and compressibility of the anatomical target can affect how one may strategize this approach (IBID). An example of this would be to take the concept of the skull, comprised of a majority of dense bone, and understand how the density of the bone affects the rate at which FUS beam can be emitted. One could infer that bone of higher density, such as the skull, would require an output of stronger force or acoustic impedance to hit a desired target.

Due to the variation in parameters based on the anatomy and tissue density there are a few interactions that take place between the FUS beams and cells that include concepts such as reflection, refraction, diffusion, and absorption (Giammalva, et al. 2021). These shifts and variations must be accounted for when utilized at altered frequencies for therapeutic purposes due to the potential destructive effect higher frequency FUS may have on the patient if not controlled properly (Baek, et al. 2022). The initial studies on FUS began in the early 1940s for cortical and subcortical ablations on mammals (IBID). Later in the 1950s researchers began to study the use of high intensity focused ultrasound (HIFU) to produce necrotic lesions in the basal ganglia of previously craniotomized animals (Giammalva, et al. 2021).

Researchers found that this HIFU approach did not affect surrounding brain parenchyma (IBID). The difference between HIFU waves and ultrasound sound waves that can be described as high frequency are important to delineate (Baek, et al. 2022). The high frequency that general ultrasound waves emit for diagnostic purposes can be

understood as a frequency greater than 20,000Hz that the human ear cannot perceive, and not harmful when used for these generally referred purposes (IBID). HIFU waves on the other hand are more localized waves, which can be higher powered at ~20 dB/cm*MHz to penetrate the skull and ~0.8 dB/cm*MHz to penetrate brain tissue (IBID). One must be able to understand the difference of ultrasound as a diagnostic tool and HIFU because neither modality functions at the same frequency or intensity.

As previously mentioned, the reflection, refraction, diffusion, and absorption are critical components to delineate for HIFU on other regions of the body as opposed to a transcranial approach (Baek, et al. 2022). The attenuation of bone within the skull and the variations in skull bone structure can yield a different reflection response commonly referred to as acoustic scattering when compared to other targeted regions of the body (IBID). Acoustic scattering occurs when the effected acoustic wave reflects off interfaces between different tissues due to variances in the density and compressibility of those structures (IBID). This essentially means that once the HIFU penetrates through the skull, the adjacent anatomical structures beneath the skull can reflect or scatter between the bone and soft tissue. HIFU utilized to treat a targeted area through the skull may require more power due to the increased attenuation of that structure (IBID). This implies that there most likely would be decreased power of heat available at the internal tissue target and increased projection of heat toward nontargeted soft tissue (IBID). Medical device technology has advanced into multiple phased-array transducers that can deliver sufficient thermal energy in a small, focused area through the skull to stimulate a controlled thermal ablation for more successful regulation of these adverse effects (Giammalva, et al. 2021).

In order to track or monitor the trajectory of these HIFU waves many clinicians utilize what can be referred to as MR-guided FUS (MRgFUS) (Baek, et al. 2022). In vitro studies with MRgFUS in 1998 showcased the simultaneous visualization of anatomical and temperature maps with feedback to complete incisionless procedural loops (IBID). This later led to the use of computed tomography (CT) as a pretreatment method to determine the skull thickness and ultimately the density of the skull to better identify the attenuation and determine energy deposition density (IBID). This essentially means that to further improve the safety and effectiveness of HIFU, researchers utilized other modalities for image overlay to measure different anatomical components like tissue and bone for the determination of a more accurate trajectory on thermal energy output for treatment on patients. This can commonly be seen in current cranial procedures, like a tumor resection or DBS case, where the clinician takes a preoperative CT and magnetic resonance image (MRI) and overlays them on top of one another. This technique allows one to determine the skull thickness or density from the CT and then coordinate the instrument trajectory through the skull and into the soft tissue of the brain seen in an MRI.

A CT scan of high resolution and the use of bone kernel for image reconstruction and representation, recognized in Hounsfield units (HUs), allows one to calculate the skull density between the mean cortical and mean cancellous bone (Baek, et al. 2022). These ratios are configured in an HIFU system which account for all rays that span the skull in a single measure called the skull density ratio (SDR) (IBID). This ratio determines the optimal thermal ablation or energy required for effective penetration, similarly seen in the example of instrument trajectory for a tumor resection or DBS

procedure. The SDR ratio index has been a common tool to determine which patients are best suited for the MRgFUS procedures (IBID). In fact, practice guidelines from the American Society for Stereotactic and Functional Neurosurgery outline that patients with <0.4 SDR index should not undergo MRgFUS procedures due to inadequate active heat at the intracranial target (IBID). This can result in an increased time to achieve the desired ablative temperature, which can then lead to unwarranted heating of nontarget tissues (IBID). The potential consideration of this procedure for patients with <0.4 SDR index would require clinicians to take into account factors such as skull thickness, incidence angle, and skull heterogeneity upon examination (IBID).

Continued research on HIFU and MRgFUS have propelled the initiation of standards aimed to help the adoption of this technology be considered as an optimal treatment modality for patients. In conjunction to the research on HIFU and MRgFUS, low frequency ultrasound has also been studied as an optimal treatment modality for neurodegenerative diseases (Baek, et al. 2022). This technique embodies a neuromodulation approach aimed to alter neuronal signals and function of targeted brain regions (IBID). Further exploration of altered frequencies used for FUS can be more thoroughly understood in later sections as the initial studies of FUS were primarily established for ablative purposes. Even though research on FUS has fluctuated overtime relative to importance, these treatment modalities have continued to become more widely considered as a tool to treat neurodegenerative diseases and can be evidenced by the approval of MRgFUS systems from the Food and Drug Administration (FDA) for the use of thermoablation in 2016 to treat essential tremor (ET) and tremor dominant PD (IBID). Further comprehension on how FUS can be utilized for the treatment of

neurodegenerative diseases such as AD, PD, and ALS, should consider current clinical uses of FUS at varied frequencies and understand how these frequencies can alter a potential treatment outcome.

Current Uses:

Current uses of FUS are important to understand as the treatment modality has become useful beyond the initial focus of ET and tremor dominant PD. Other FUS applications in either high or low intensity or MRgFUS treatment methods allows for further support of the technology, the adaptability, and future capabilities on how these techniques can continue to be incorporated as a non-invasive treatment modality for patients. Ultimately, this non-invasive approach cannot only help to treat patients, but increase their quality of life through the reduction of common risks and variables typically seen in other parallel invasive approaches. Some of the current uses of HIFU, low intensity focused ultrasound (LIFU), and MRgFUS can be seen in treatments such as obsessive-compulsive disorder (OCD), neuropathic pain, the treatment of brain tumors, impaired consciousness, epilepsy, and even depression (Baek, et al. 2022; Hosseini, et al. 2022; Hu, et al. 2023).

More specifically, some of these current treatments are identified as FUS with a transcranial approach similarly described in the diagnostic section for transcranial ultrasound techniques. The transcranial approach simply refers to the location where the use of the ultrasound device may be referenced, like the cranial region. Some studies reference FUS approaches like LIFU and HIFU and transcranial may not be specified in the name, but can be determined through the description of the intervention. In some cases, the term transcranial can be seen in the named FUS technique like low intensity

transcranial ultrasound stimulation (LITUS) and transcranial MR-guided focused ultrasound (tcMRgFUS) (Hu, et al. 2023 & Giammalva, et al. 2021). The specific FUS terminology can be important to understand, as certain studies can reference these applications differently relative to the treatment and target region.

Some psychiatric disorders such as OCD can present in medication resistant forms (Baek, et al. 2022). One study comprised of 4 patients with medication resistant OCD, bilateral MRgFUS was used to create lesions in the anterior limb of the internal capsule, which resulted in a mean improvement of 33% over a 6-month follow-up (IBID). Additionally, depression and anxiety levels were reduced by 69.4% (IBID). The neurophysiology of OCD has been shown to be associated with an overactivation of the cortico-striatal-thalamo-cortical (CSTC) connectivity loops, and the anterior internal capsule remains one of the notable regions within that loop (Hosseini, et al. 2022).

MRgFUS has been shown to be utilized in clinical trials to treat neuropathic chronic pain as of recent (Baek, et al. 2022). A crossover study for the use of MRgFUS to treat neuropathic chronic pain remains in progress, which makes the results not yet available; however, the focus of this randomized, sham-controlled, cross over study aims to examine the safety and effectiveness of the MRgFUS lesion procedure for the treatment of chronic pain (IBID).

Blood brain barrier (BBB) accessibility with the use of FUS for the treatment brain tumors has also gained traction as of recent (Hosseini, et al. 2022). A few studies discuss how current methods of FUS as a treatment modality for brain tumors temporarily causes a micro disruption of the BBB when LIFU, HIFU, and or MRgFUS are used (IBID). However, some research suggests that LIFU may be the most optimal

method for the treatment of brain tumors, as HIFU can result in an increased risk for hemorrhage and edema (Baek, et al. 2022 & Hosseini, et al. 2022). The purpose of a FUS approach to treat brain tumors requires FUS to penetrate the BBB for more effective chemotherapy treatment and drug delivery methods (Baek, et al. 2022). Additionally, penetration of the BBB through the use of LIFU coupled with intravenous microbubbles was shown to open the BBB in rabbits without producing any neuronal damage (IBID). The first-in-human trial of noninvasive MRgFUS BBB opening in malignant glioma patients, with paralleled administration of chemotherapy drug delivery showed an increase of 15% to 50% signal enhancement in T1-weighted magnetic resonance images (IBID). This means that the increased uptake of the chemotherapy drug was visible in the weighted magnetic resonance images and could therefore be calculated.

Researchers verified these calculations through the measurement of chemotherapy concentrations in sonicated and unsonicated tissue samples after the tumor resection completion (Baek, et al. 2022). Essentially, this study shows the comparison between one sample group that had removal of tumor tissue previously treated with LIFU coupled with chemotherapy drug delivery and another group that had removal of tumor tissue not previously treated with FUS, but did receive chemotherapy in another administered method (IBID).

The results showed that the chemotherapy concentration was 7.7 times higher in the tumor tissue removal group that received LIFU, and chemotherapy compared to the group that did not receive LIFU, but did receive another administered form of chemotherapy (IBID). One observation important to note through the analysis of studies that utilize HIFU and LIFU, remains centered around the fact that HIFU typically results

in cell death or tissue that becomes necrotic due to the thermal ablative approach, which can present as damaged tissue or a lesion, whereas LIFU may be more utilized to modulate biological effects similarly seen with BBB intervention.

LIFU current uses also reach into areas such as treatment for impaired consciousness (Baek, et al. 2022). A study done in 2016 showed score improvements in the Glasgow Coma Scale and Coma Recovery Scale-Revised aimed to assess levels of consciousness, for a patient that suffered from posttraumatic disorder of consciousness (IBID). This patient received 10 pulsed sonications at a low frequency to the thalamus in 30 second intervals (IBID). The patient attempted to walk and demonstrated new motor responses and vocalization five days after treatment (IBID). The focus of this treatment was localized to the thalamus given the perceived role of this anatomical region in coordination of awake and sleep states (IBID). In addition, LIFU has been utilized to treat mood disorders, with some studies that show after FUS treatment to the right inferior frontal gyrus, patients presented with a significant mood enhancement for up to 30 minutes after treatment (IBID). These outcomes demonstrate that the use of LIFU was able to temporarily alter brain function and connectivity to yield positive results and advancements in a patients' treatment trajectory.

Similarly related to the outcomes of LIFU for mood enhancement, LIFU has also been utilized to treat depression (Hu, et al. 2023). Some patients that suffer from depression can experience failed responses to treatment or even adverse effects, which limit their chances of a successful outcome (IBID). The stimulation effect of LIFU has been shown to enhance brain-derived neurotrophic factor (BDNF) levels in rodent models, which can typically present in a downregulated state for individuals that suffer

from depression (IBID). Researchers have also found that LIFU stimulation has the ability to significantly reduce lipopolysaccharide-mediated upregulated inflammatory cytokines in depressed mice (IBID). This shows that LIFU stimulation can alter biological effects of certain states in varied diseases and disorders associated with emotional impediments. Relative to the data that surrounds BBB opening, common drug treatments for depression remain centered around the drug's permeability to cross the BBB. Through the assistance of LIFU, more successful treatment outcomes may be possible.

The data and outcomes of these studies are pertinent to preclinical and clinical experiments, which means there still may be more research that needs to be completed for the treatment of FUS to be FDA cleared on humans as a clinical application. The results of these studies demonstrate FUS as a favorable future treatment that remains non-invasive and can be initiated as part of an earlier treatment intervention for more successful patient outcomes.

tcMRgFUS, a form of FUS was briefly referenced and described as an MR focused form of FUS with an application isolated to the transcranial region. More specifically, this form of FUS cab be understood as a procedure that drives focused ultrasound beams towards a therapeutic target while the skull remains fully intact (Giammalva, et al. 2021). Unlike some of the other uses of FUS, this neurosurgical application has been successfully adopted for procedures such as thalamotomy, pallidotomy, and subthalamotomy as a non-invasive technique to treat movement disorders (IBID).

Other areas of exploration include drug-resistant epilepsy, drug-resistant trigeminal neuralgia, chronic neuropathic pain, psychiatric disorders, ischemic and hemorrhagic stroke, and progression in neuro-oncology (Giammalva, et al. 2021). This technology and approach are similar to what has been previously outlined relative to frequency and intensity fluctuations of FUS beams, however, the terminology highlights a focus on the transcranial methodology. The principal focal points of either thermal ablation, neuromodulation of biological effects, and or BBB permeability, are the foundational mechanisms that translate into the tcMRgFUS treatment modus for the aforementioned areas of current use.

Focused Ultrasound for Neurodegenerative Disease Treatment

The use of FUS for neurodegenerative disease treatment has been more commonly studied for diseases like AD and PD compared to that of ALS shown in a systematic review (Hu, et al. 2023). Various research suggests the most common uses of FUS for the treatment of neurodegenerative diseases are neuromodulation techniques that either utilize LIFU or HIFU to modulate dysfunctional neuronal processes due to the disease or to open the BBB (Baek, et al. 2022). BBBO is a form of neuromodulation where altered frequencies of FUS are used to manipulate the permeability of the BBB for more effective drug delivery without the production of damaged tissue seen in more ablative techniques from higher FUS frequencies (Miller and O'Callaghan, 2017; Baek, et al. 2022).

Other neuromodulation techniques target more excitatory or suppressive functionality of the central nervous system (CNS) or peripheral nervous system (PNS) in order to try and regulate inflammatory responses to proinflammatory cells, increase

neurotransmitter and neurotrophic factor levels, and ultimately slow the progression of these diseases (Dell'Italia, et al. 2022 & Zhong, et al. 2023). The lack of outlined treatment protocols and studies that identify exact measures for neuromodulation approaches and BBBO for AD, PD, and ALS remain a challenge for each of these targeted FUS therapies. Although there are studies that showcase how these techniques have been used and modified in rodent models, limited studies highlight the strong effectiveness for all three disease pathologies. The successes that have been identified for each will be outlined in the sections to follow. These sections can bring to light what data has been collected and established for AD, PD, and ALS in the areas of FUS for neuromodulation and BBO, to place further emphasis on where future research may be headed. Researchers will need to capitalize on the successes of these studies so that more standardized practices can be established as these conclusions carry into further placement of human trials.

Neuromodulation

Neuromodulation can be referred to as a bioelectronic technique that artificially manipulates nerve activity and function (Fu, 2023). This type of neurotechnology exhibits modulation effects in the CNS and peripheral nervous system (PNS) by mode of physical or chemical methodology (IBID). Neuromodulation can control and regulate specific neuronal excitability and neural circuit conduction through the physical effects of FUS (Chen, et al. 2021). Dysfunctionality of neural circuits appears to be a common theme in neurodegenerative diseases, which can result in impaired cognitive, sensory, or motor function (IBID). FUS as a neuromodulation technique has been shown to be a reversible method to either stimulate or inhibit nervous system activity (IBID).

As previously mentioned in the focused ultrasound mechanics section, certain applications of FUS use varied frequencies to either target specific tissue regions for a neuromodulated non-thermal method of treatment, aimed to preserve the targeted and adjacent tissue, or can be used as a more aggressive thermal technique tailored towards ablation of targeted tissue to create a lesion (Darrow, 2019). The difference in these methodologies remains important to distinguish for the determination of the type of FUS that should be utilized as the most optimal treatment modality for neurodegenerative diseases. HIFU can produce permanent lesions within in the brain through a controlled thermal ablative approach, while LIFU has been shown to reversibly excite and inhibit neural activity (IBID). Technically, both HIFU and LIFU can be seen as a neuromodulation technique given that they both alter the state of neural activity within the brain. The use of FUS for BBBO can also be referred to as a neuromodulation technique, however, given the complexity and focus of the BBBO method a separate review will be outlined in later sections.

Transcranial focused ultrasound (tFUS), a form of FUS that has been studied for neuromodulation also has the potential to alter sensory and motor functionality within the brain (Zhang, et al. 2021). The terminology of tFUS may be used interchangeably in reference to other FUS techniques with the main difference central to the targeted treatment region. A lot of studies use interchangeable terminology for FUS and the core context of the FUS approach remains positioned in the description of the FUS technique. This can be seen in a systematic review by Zhang and colleagues, which focused on ways tFUS has been shown to produce excitatory and inhibitory effects within the cortex, deep brain areas, and the thalamus (IBID).

Although this review appears quite detailed, the conclusions drawn among the various scholars shows how tFUS at varied frequencies had the ability to initiate a controlled neural response, like modulated neural oscillation to inhibit seizures in mice or heighten sensorimotor performance in photothrombotic stroke mice (Zhang, et al. 2021). Even though these examples are not directly focused on AD, PD, or ALS specifically, the neural network overlap that can propagate among these varied neurological conditions pose hopeful aid in the use of FUS treatments like tFUS for neuromodulation of associated neural circuits and parallel networks in neurodegenerative disease.

Most neurodegenerative disease focus remains relative to the degradation of neuronal components as the disease progresses overtime. One benefit that neuromodulation can also provide can be seen in neurotrophic factor manipulation (Chen, et al. 2021). Polypeptides also known as proteins are neurotrophic factors that have the ability to promote survival, growth, and differentiation of nerve cells (IBID). Research has found FUS can foster the release and delivery of neurotrophic factors such as BDNF, glial cell-derived neurotrophic factor (GDNF), and vascular endothelial growth factor (IBID). One study showed that these specific neurotrophic factors were increased after LIFU stimulation of the integrin receptors (IBID). This highlights how FUS can potentially be utilized as a neuromodulation technique to force the initiation of cell growth or the release of critical components within associated neurodegenerative disease neural networks to help reverse primary contributors to these disease progressions.

Alzheimer's Disease and Neuromodulation:

The neuromodulation techniques for AD can mirror similar approaches utilized for BBBO. Some research has shown that focused ultrasound with microbubbles (FUS-

MB) not only helps to open the BBB, but also can reduce Aβ plaques and surface area without additional therapeutic agents (Hu, et al. 2023). In transgenic AD models such as TgCRND8, 3xTg, and 5xFAD, stimulation to the hippocampus, cortex, and whole brain through the use of FUS-MB showed Aβ clearance success as the only intervention (IBID). Mouse models like 5xFAD with more severe amyloid pathology, showed FUS targeted at the whole brain improved cerebral blood flow, which in turn improved cognitive impairments effected by poor cerebral blood flow (IBID).

This result links back to the research supporting TCD as a potential diagnostic tool to measure cerebral blood flow in the brain as a potential indicator of AD (Roher, et al. 2011). The results which showed an improvement in cognition and cerebral blood flow with the use of FUS in the 5xFAD mice, validates the research that Roher and colleagues support relative to how cerebral blood flow may be affected in AD, and therefore justifies why TCD would be a valuable diagnostic tool (Hu, et al. 2023 & Roher, et al. 2011). The use of two different forms of ultrasound can ultimately be utilized to confirm the same findings, that cerebral vascular flow may be indicative of the AD pathology.

The systematic review by Hu and company also highlighted a study that found reduction in Aβ plaque size in TgCRND8 mice when FUS was used to stimulate the hippocampal region (Hu, et al. 2023). Others support this data and have also highlighted how not just FUS, but FUS-MB can modulate the expression of genes associated with Aβ production, which in turn can aid in the reduction of Aβ plaques shown to be correlated with behavioral changes associated with improved function (Hosseini, et al. 2022). Similarly, in 5xFAD mice one study used acute FUS to stimulate the hippocampus and

found that this technique had the ability to not only reduce Aβ plaques, but actually increase the number of microglia nearby the Aβ plaques (IBID). These studies used LITUS or a lower intensity form of FUS to treat the transgenic mouse models and explained how the reduction in Aβ plaques could have been attributed to the increase in production of Aβ antibodies that were bound to the plaques in the cortex of the TgCRND8 AD mouse models (IBID). Another plausible explanation for these outcomes could be that LITUS stimulated phagocytosis of the Aβ protein through microglial activation, however, other studies have shown limited increase in inflammatory response of other transgenic AD mouse models, which makes this explanation controversial to different pathological variants (IBID).

One observation shows how a majority of TgCRND8 transgenic AD mouse models treated with FUS yielded stronger outcomes, which includes an increase in the number of immature neurons, total dendrite length, and dendrite branches in the neurons of these types of mice (Hosseini, et al. 2022). The variability between the different mouse models will need to be further investigated to validate efficacy, but overall, this research shows that FUS as a neuromodulation technique for stimulation of particular anatomical regions affected by AD has the potential to produce successful outcomes at least temporarily, in the regression of AD disease progression.

In order for these studies to show valued effect on human participants more research must be performed to determine the success rate of these results over time. Researchers will need to understand how the protocols used in these mouse models would translate on human AD patients and how the efficacy of this treatment overtime may present. The data within the systematic review by Hu and colleagues outlines where

the future of AD treatment can be as researchers move from transgenic mouse models to human trials.

The use of low intensity or low frequency focused ultrasound, which includes FUS-MB has also been shown to increase neurotrophic factor levels like BDNF, associated with the process of neurogenesis, neuroplasticity, synaptic plasticity, and memory (Hosseini, et al. 2022). In AD patients, BNDF levels have been shown to be reduced and could play a large role in the disease progression (IBID). Many studies outline the use of FUS-MB to increase BBB permeability for the administration of BDNF gene therapy as a potential treatment option to reverse neural circuit and network atrophy and dysfunctionality (IBID). However, some studies have even shown that FUS-MB without the administration of BDNF still upregulated BDNF levels in localized brain regions (IBID).

In addition, FUS-MB has the potential to upregulate vascular endothelial growth factor (VEGF) to assist in the formation of new blood vessels (Hosseini, et al. 2022). This again supports the data that vasculature remains highly affected in AD patients and could potentially be viewed as a diagnostic indicator given that some FUS practices target neural and cellular components correlated with cerebral vasculature as a potential treatment for AD disease management. FUS-MB can also aid in new neuron growth through upregulation of GDNF, endothelial nitric oxide synthase, nerve growth factor, and basic fibroblast growth factor (IBID).

Together between the gene alteration effects of neuromodulation and the initiation potential for new vascular and neuronal growth, FUS-MB at lower frequencies can potentially help deliver AD treatment in a less invasive way and may even be just as

effective as BBBO AD treatments with exogenous drug administration. Studies that targeted the hippocampus with low intensity ultrasound pulses further support this, as they found this technique increased neural activity and network movement, which mirrors hippocampal circuit activation (Hosseini, et al. 2022). This clinical study comprised of AD patients, validated their discoveries with functional MRI to confirm improvement in areas of memory and verbal processes, which were maintained up to three months post FUS treatment (IBID). This shows the potential for FUS as a patient centric treatment modality with favorable success that still upholds the patient's quality of life.

Parkinson's Disease and Neuromodulation:

Various studies as of recent, focus on the use of FUS as a treatment modality for individuals with PD. Some of these studies include how HIFU, LIFU, and LITUS can either be utilized as an ablation or neuromodulation technique for anatomical regions in the brain such as the ventral intermediate nucleus of the thalamus (Vim), thalamus, subthalamic nucleus, globus pallidus interna, and cuneiform nucleus (Hu, et al. 2023; Zhong, et al. 2023; Miller and O'Callaghan, 2017). Forms of FUS such as MRgFUS and more specifically tcMRgFUS have also been highlighted in recent studies (Lu, et al. 2023 & Lin, et al. 2022). The wide range of neuromodulation focal points for the treatment of PD with FUS offers a number of potential advancements and avenues for researchers to capitalize on while a cure for PD remains under development.

A current invasive treatment option for PD that aims to minimize tremors can be referred to as DBS, which involves the implantation of electrodes to specific brain regions (Hu, et al. 2023). Although this treatment has been shown to be effective for the reduction of adverse involuntary motor effects of PD and side effects relative to long-

term dopamine replacement drugs like Levodopa, this invasive treatment option still poses a significant risk of infection and cerebral hemorrhage to the patient (IBID). Long-term dopamine replacement drugs can also cause side effects, which implies that neither option may truly be ideal in terms of patient quality of life. HIFU and MRgFUS are alternative approaches that may help to achieve the same type of lesion outcome seen with DBS and still reduce dyskinesia symptoms induced by Levodopa long-term, as they have been found to be successful in recent studies (Baek, et al. 2022).

In 2018 the FDA approved the use of HIFU for the ablation of Vim in patients with tremor dominant PD (Baek, et al. 2022). The HIFU waves were used to permanently damage the targeted tissue and create an irreversible lesion on the thalamic Vim structure (IBID). Results of the randomized controlled trial showed significant tremor suppression from the ablation with HIFU and MRgFUS (IBID). Patients showed improvements in the finger-to-nose point tasks and a reduction in the clinical assessment score for tremor (CRST) by 81.3% at 3 months post treatment compared to baseline scores (IBID). Additionally, another study utilized MRgFUS in a Vim thalamotomy, also understood as an ablative technique for the isolated region in the thalamus with FUS, for patients with PD and Levodopa refractory (IBID). Results showed a 62% improvement in CRST scores for hand tremor opposite to the treatment side (IBID).

These results indicate that long-term dopamine replacement drugs have the ability to become ineffective overtime, while also can result in adverse effects like dyskinesia. Likewise, even if DBS results demonstrate the same effectiveness or potentially more successful outcomes compared to FUS, the results seen from non-invasive FUS ablative techniques have demonstrated a 50% improvement rate in CRST scores with reduced

adverse risks, which essentially shows how FUS can achieve the same desired effect as the DBS approach. This can be further supported by another study that showed 55.9% improvement in CRST scores at 3 months post-treatment in six patients with various tremor types (Baek, et al. 2022).

The population size of this specific study appeared small and two of the patients experienced long-term side effects of tongue numbness and one-sided muscle weakness with reduced sensitivity unilaterally; however, these side effects compared to a prolonged tremor, potential cerebral hemorrhage or infection as a result of the DBS procedure, or even refractory of a dopamine replacement drug with an induced adverse effect of dyskinesia, result in far less debilitation relative to a patient's overall quality of life with progressive PD symptoms. In fact, in a ten-patient population HIFU and MRgFUS study, one of the patients developed dysarthria and right motor hemiparesis because of the off-target effect of the internal capsule in the FUS beam and was found to be recovered 2 days post-surgery (Lu, et al. 2023). This shows that the potential side effects of FUS may even be somewhat temporary, especially since the "long-term" side effects referenced appear vague and lack support of a chronological timeline.

Some of the main areas of interest for HIFU ablation with MRgFUS consist of the internal globus pallidus, pallidothalamic tract, Vim, and subthalamic nucleus (Lu, et al. 2023). The internal globus pallidus relays information from the striatum, globus pallidus externus, and subthalamic nucleus to the thalamus (IBID). Dysfunction of the internal globus pallidus can lead to dystonia or involuntary muscle contractions in PD patients (IBID). The use of MRgFUS for targeted ablation of the internal globus pallidus has been shown to be effective for the improvement of patients' movement disorders (IBID). More

specifically, HIFU with MRgFUS was successful in eight out of ten patients not on PD medication and showed significant improvement of the Parkinson's Disease Rating Scale (UPDRS) and Unified Dyskinesia Rating Scale scores by 32.3% and 52.7% at the 6-month follow-up (IBID). The suppression of over-inhibited thalamic output from the globus pallidus can also be accomplished with HIFU and MRgFUS (IBID). Results of this clinical study showed improved UPDRS and global symptom relief by 60.9% and 56.7% at the 3-month follow-up (IBID).

Additionally, patients affected by tremor dominant PD typically have relay malfunction of the Vim, which transmits information through the striatal-thalamocortical and cerebello-thalamocortical circuits (Lu, et al. 2023). MRgFUS ablation for this targeted region has been shown to be effective in the improvement of CRST scores for hand tremor and UPDRS motor scores by 62% and 8 points at a 3-month follow-up (IBID). Lastly, MRgFUS ablation targeted at the subthalamic nucleus has also been shown to reduce abnormal movements of PD with a study that showed improved UPDRS scores by 53% from baseline to 6-months in the non-medication group compared to 47% improvement from baseline to 6-months in the medication group (IBID). This data presents significant discoveries in the effectiveness of HIFU and MRgFUS as an ablative technique for the treatment of patients with PD. One could compare success rates and adverse outcomes in DBS procedures and dopamine replacement drugs to HIFU and MRgFUS treatment modalities to further advance the efficacy of these studies.

Neuromodulation techniques have been shown to be successful with LIFU and LITUS. Essentially, LIFU and LITUS can be interpreted as one in the same as they both utilize low frequency ultrasound waves as the foundational technological element. The

delivery for these forms of FUS can typically be represented as a constant beam or through consecutive pulses (Zhong, et al. 2023). Relative to PD, LIFU has been shown to stimulate astrocytes in the motor cortex of the subthalamic nucleus and help to promote the release of neurotrophic factors (IBID).

Similarly, LIFU has been shown to elicit an inhibitory effect on cytotoxic cerebral edema, which demonstrates therapeutic potential in the reduction of localized AQP4 around astrocyte feet (Zhong, et al. 2023). This means that LIFU can help regulate neuronal factors that influence neuroinflammation. Research has shown that neuroinflammation can be a relative component involved in PD, but has not yet been fully understood (IBID). The effects of neuromodulation are closely tied to the intensity, frequency, stimulation duration, and duty cycle of FUS proliferation and because there are currently no standard protocols established, much of the research still remains in animal models (IBID).

PD mouse models induced with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes a syndrome that mimics dopaminergic degeneration seen in PD and common neurological symptoms (Hu, et al. 2023). Researchers found that MPTP induced mice treated with LITUS exhibited signs of improved locomotor behavior due to the stimulation of the subthalamic nucleus and globus pallidus (IBID). Furthermore, LIFU was shown to regulate normal levels of neurotrophic factors, dopamine transporters, and tight junction proteins in the BBB of induced PD mice (IBID). The modulation techniques of LIFU in the alteration of cortical excitability makes this a significant result (IBID). Overall, low frequency ultrasound and stimulation was shown to weaken dopaminergic neurodegeneration, locomotor insufficiencies, and alter extracellular

concentrations of dopamine and serotonin in PD mouse models (Hu, et al. 2023 & Zhang, et al. 2021). The main pathological shifts in the PD pathology typically present as a loss of dopaminergic neurons in the substantia nigra, which means that any neuromodulation approach with LIFU that can manipulate and alter the dysfunctional neural activity which contributes to this loss without the result of further cellular damage, adds value to the advancements of future PD treatment research.

Amyotrophic Lateral Sclerosis and Neuromodulation:

Limited research exists that showcases the neuromodulation effects of FUS on ALS. There are commonalities that overlap relative to the pathology of the disease and other neurodegenerative diseases, which allows for scholars to pose plausible possibilities despite a lack of current data. Evidence that supports the use of FUS as a neuromodulation technique for PD, creates parallels that can be explored for ALS, which may help to define a theoretical foundation for future ALS and FUS research that highlights the neuromodulation effects and techniques (Lu, et al. 2023).

Prell, et al. found that of the ALS subjects where the lamellar structures were imaged with transcranial sonography, 70% showed hyperechogenicity of the substantia nigra, similar to outcomes indicative of PD (Prell, et al. 2014). Additionally, 47.9% of ALS patients imaged in this study showed hyperechogenicity of the brainstem (IBID). This remains an important discovery because in a 9-year case duration referenced by Suzuki, et al. where ALS genetic variants were discussed, researchers found that along with usual discoveries of ALS, histological examination showed atrophy of midbrain capsules, widespread neuronal loss of the substantia nigra, nucleus accumbens, subthalamic nucleus, and the globus pallidus (Suzuki, et al. 2023).

The paralleled findings in the Suzuki, et al. referenced case for ALS and the systematic review by Lu, et al. which highlights neuromodulation techniques through the use of MRgFUS for PD which focused on targeted regions like the internal globus pallidus, pallidothalamic tract, Vim, and subthalamic nucleus whose circuitry directly effects activity in the substantia nigra, allows one to form a theory that the current uses of MRgFUS for PD may also be plausible for cases like ALS (Suzuki, et al. 2023 & Lu, et al. 2023). The subthalamic nucleus in PD cases remains a target because of the observed overactivity due to the loss of dopamine (Lu, et al. 2023). This overactivity in turn increases the activity of the substantia nigra and internal globus pallidus, which directly effects cortical motor activity (IBID).

This synchronously validates the results in Prell, et al. where hyperechogenicity of the substantia nigra was seen in the transcranial ultrasound images, congruent with images of PD patients (Prell, et al. 2014). The argument can be made that if the loss of dopamine increases activity in the substantia nigra and has also been shown to decrease cortical motor activity, and LITUS has been shown to stimulate the release of dopamine to regenerate dopaminergic neurons in PD mouse models, then neuromodulation techniques of LITUS could be used to yield similar results in patients with an ALS pathology (Lu, et al. 2023 & Zhang, et al. 2021).

Additionally, researchers have found that cortical hyperexcitability has been shown to be part of the ALS disease evolution over time, which affects cortical motor activity in both upper motor neurons and lower motor neurons (Menon, et al. 2020 & Hu, et al. 2023). LIFU studies for the treatment of PD have indicated how the use of FUS at a lower frequency can potentially alter cortical excitability, which correlates how these

overlapped results could be used for ALS neuromodulation use case justification (IBID). This means that ablative or stimulation techniques with FUS for neuromodulation found to be successful in PD studies may also be valuable to explore for ALS cases. There are no current research studies that explicitly state how these neuromodulation techniques are specifically used for ALS; however, the connections that can be drawn between the effected regions in both PD and ALS cases pose possibility for future consideration.

Approximately 90% of ALS cases are sporadic, however, there are also genetic mutations like SOD1 and TDP-43 that effect some ALS patients (Monsour, et al. 2022). In addition, motor neuron degeneration theories have been comprised of many factors with the main commonality shown to be associated with the neurovascular unit (IBID). The neurovascular unit consists of neurons, glial cells, endothelial cells, vascular smooth muscle cells, pericytes, and a basement membrane which makes this important to note (IBID). In the ALS pathology, lymphocytes, pro-inflammatory cytokines (IL- 1α, IL-1β, TNF-α, and IL-1RA), proinflammatory enzymes (COX-2), and IgG relative to immune response were shown to be increased in cerebral spinal fluid in the spines of ALS patients (IBID). The evidence that supports an increase of these cellular components as a part of the ALS pathology relative to the process and mechanism still remains highly unknown (Nango, et al. 2023). Current research suggests that neuroinflammation contributes to motor neuron degeneration seen in the elevated release of pro-inflammatory cytokines and enzymes in ALS cerebral spinal fluid, as well as increased numbers of microglia and reactive astrocytes, most likely initiated as a combative response to the neuroinflammatory contributors (IBID).

ALS findings support widespread neuronal loss of the subthalamic nucleus, which effects substantia nigra neuronal activity and the association of these locations to motor response, which allows one to infer that treatment of this area could potentially improve the current cellular cascade outcomes seen in the ALS pathology (Suzuki, et al. 2023 & Zhong, et al. 2023). The disease pathology parallels already established between PD and ALS in conjunction to the successful outcomes seen with LIFU and PD in the modulated expression of astrocytes, microglia, and anti-inflammatory cytokines, poses the potential for similar success in ALS neuromodulation with FUS (Zhong, et al. 2023 & Monsour, et al. 2022). In a systematic review of FUS and ultrasound stimulation treatments for PD, researchers found that continuous ultrasound deep brain stimulation on the subthalamic nucleus and globus pallidus for 5 weeks in MPTP PD mouse models showed that this treatment improved motor function and reduced microglia and astrocyte inflammatory responses (Zhong, et al. 2023).

Additionally, DBS of the subthalamic nucleus yielded inhibitory microglial activation of the substantia nigra, which resulted in more regulated expression of pro-inflammatory cytokines (Zhong, et al. 2023). This shows that stimulation of these regions has the potential to reduce neuroinflammation in these areas and normalize the expression of certain pro-inflammatory factors in PD. Furthermore, the overlap seen relative to commonalities amongst ALS studies, allows one to infer that the integration of similar treatment models may be possible to produce similar patient outcomes. PD studies with HIFU have shown similar effectiveness for tremor suppression like DBS for isolated regions of the thalamus like the Vim structure, which further supports these conclusions and claims (Baek, et al. 2022).

Overall, more research needs to be completed for ALS and FUS for neuromodulation, however, current practices and outcomes seen in PD may prompt initial exploration. There are limited studies and data that showcase the effects of ALS and FUS for neuromodulation, but a practical place to start would be to study the various forms and frequencies used for FUS in an ALS diseased rodent model. This would allow researchers to understand how manipulations of FUS alone effect the ALS pathology to then determine how FUS could be properly utilized either alone or in combination with other therapeutics.

Opening Blood-Brain Barrier (BBBO)

The blood-brain barrier consists of endothelial cells, pericytes, and astrocyte end feet that border cerebrovascular structures and regulate the exchange of cellular components between the brain and circulatory system (Noel, et al. 2023). Notice how the context of cerebrovascular structures has appeared again in the treatment modality texts of FUS and the BBBO. Paralle connections between the use of TCD to identify neurodegenerative diseases and FUS as a treatment modality for BBBO are centered around cerebrovascular functionality and structure. This supports the evidence of TCD as a diagnostic modality because with the conclusions centered around how cerebrovascular structures are affected in patients that suffer from neurodegenerative diseases together with the studies that identify FUS as a treatment modality for earlier drug intervention through the BBBO one can recognize how TCD could be integrated. The BBB consists of cells and other cellular structures that surround cerebrovascular structures and even regulate the exchange between the brain and circulatory system, which allows to infer that therapeutic intervention with the use of FUS to temporarily increase BBB

permeability can have a direct effect on the cerebrovascular functionality and structures negatively impacted by neurodegenerative diseases. This may even have the potential to reverse or reduce circulatory complications evident in patients that suffer from neurodegenerative diseases such as AD, PD, and ALS.

The main goal of the BBB remains centered around the protection of the central nervous system (CNS) from circulated pathogens and other damaged species (Noel, et al. 2023). The BBB acts as a highly restrictive barrier, which regulates what passes through (IBID). This is turn results in BBB inhibition of approximately 98% of small molecule drugs and a majority of large molecule drugs (IBID). This presents as an enervated obstacle in the effectiveness of drug therapeutics for the treatment of neurodegenerative diseases. Restrictive properties of the BBB are important for the protection of the CNS; however, the selective properties can make this process difficult for the intervention of drug therapeutics as the regulatory effects of the BBB can limit the rate or amount of therapeutic that enters the cerebral vasculature system, which minimizes the effectiveness of drug delivery.

On the contrary age can increase cerebral permeability and can increase the degradation of tight junction proteins, responsible for the structure maintenance of organized endothelial cells and the regulation of paracellular transport over the barrier (Noel, et al. 2023). Endothethial cells, mural cells, immune cells, glia and neural cells, all work together to regulate and maintain the BBB and are identified as the neurovascular unit (NVU) (IBID). This means that the cellular components that make up the NVU work to regulate the BBB and the cerebral vascular flow. Similar groundwork was laid in the use of TCD as a diagnostic tool section, which focused on the identification of

cerebrovascular functionality and the differences between patients with neurodegenerative diseases and healthy controls (Roher, et al. 2011). The conclusions drawn from these studies highlight how cerebral vascular flow can decrease with age and can be seen to be depleted two times greater in regions associated with neurodegenerative diseases such as AD (Graff, et al. 2023).

Based upon the knowledge of the BBB and the correlation to cerebrovascular flow, one may find how the increased cerebral permeability may be important to understand, as this provides insight into the structural and neural changes that occur due to age, like decreased cerebral blood vessel density, endothelial dysfunction, arterial stiffening, and stunted vascular repair, which can affect effective drug delivery in FUS BBBO treatment modalities (Noel, et al. 2023). In normal BBB and NVU functionality the permeability of the BBB remains highly restrictive as a protective mechanism, the goal of FUS would be to increase the BBB permeability to initiate more effective drug delivery (IBID). However, some evidence shows how age and neurodegenerative diseases can ultimately affect optimal cerebrovascular flow due to the degradation of cellular components and proteins, which can in turn increase permeability of BBB and cause a breakdown of this structure. This means that FUS treatment for BBBO may not always be necessarily targeted to break the BBB, but to actually target these degraded cellular components to protect or restore BBB functionality (IBID). The use of FUS as a treatment modality to increase therapeutic effectiveness across the BBB will be explored for AD, PD, and ALS, to better understand how this non-invasive and patient centric approach can be advantageous for the deceleration of these disease progressions.

Alzheimer's Disease and BBBO:

Drug therapy can be seen as the main therapy for AD at current, however, there still no cure remains (Hu, et al. 2023 & Hoessini, et al. 2022). The hinderance of the BBBO has resulted in low efficacy of drugs to enter the brain (Hu, et al. 2023). Researchers have developed an anti-Aβ antibody to help clear the Aβ loads and plaques in patients with AD, however, researchers have also found that this treatment method has demonstrated limited ability to permeate the BBB (IBID). The use of FUS has been recently studied and proposed as a possible treatment method to increase BBB permeability for more effective drug delivery. The argument that cerebrovascular effects of AD on BBB permeability are hindered due to lack of permeability resistance as a result of degradation of the BBB, can be resolved with the support of Hosseini and colleagues, which provides support for the opposed viewpoint from studies of AD mouse models and control mice that showed there was not a significant difference in BBB permeabilization, which suggests that the degree of BBB dysfunctionality seen in some patients with AD may not be variable relative to drug treatment delivery (Hosseini, et al. 2022).

FUS has been shown to initiate BBBO and increase BBB permeability in a safe and reversible way (Rezai, et al. 2022). The key indication of BBBO remains relative to the reversibility of the structure when controlled with FUS. The BBBO needs to follow with a proper close to prevent any unwanted pathogens or damaged cellular agents, which makes this important to note. One study advanced previous outcomes that only focused on successful BBBO in the hippocampal and entorhinal cortex with FUS in patients with mild AD and was able to show that the BBBO with FUS can be safely repeated and

reproduced in various cortical and subcortical regions in larger volumes for patients with AD (IBID). Each location or region was precisely and accurately targeted to guarantee adequate BBBO and close without unwanted exposure of pathogens (IBID). In this study the BBBO was reversed within 24-48 hours after each subsequent FUS treatment, with an 82% success rate of targeted BBBO regions evidenced through quantifiable data (IBID). This shows that the effectiveness of FUS for BBBO in various regions of the brain was advantageous for therapeutic drug delivery techniques.

Now that baseline knowledge has been established on how FUS can be beneficial in BBBO for AD and can be supported by data that demonstrates the potential effectiveness for therapeutic drug delivery, a deeper exploration of the types of FUS and specific drug treatment modalities should be discussed. A few forms of FUS treatment for BBBO have been studied for AD that include focused ultrasound with microbubbles (FUS-MB) and LITUS with microbubbles (Hosseini, et al. 2022 & Hu, et al. 2023). FUS-MB involves the focus of acoustic pressure within a targeted region of the brain where the focused pressure waves interact with lipid-shelled, gas-filled microbubbles that pass through the targeted region and cause cavitation and disruption of adjacent vascular structures and tight junction protein structures, which ultimately increases BBB permeability (Noel, et al. 2023).

The mechanism of FUS-MB has the ability to potentially increase more accurately targeted drug delivery when combined with intravenous immunotherapy, which increases efficacy, and decreases toxicity (Hosseini, et al. 2022). Hosseini and colleagues highlight how FUS-MB therapy in combination with intravenous immunotherapy of anti-Aβ IgG significantly enhanced drug delivery to targeted regions,

and also significantly reduced the number, size, and surface area of Aβ plaques compared to intravenous anti-Aβ IgG administration alone (IBID). In one study, mice that received the combination of FUS-MB and IVIg to target the bilateral hippocampus showed a significant increase of hippocampal delivery at a lower dose compared to mice who only received IVg (IBID). Mice in the IVg only group did not show a significant delivery across the BBB even at higher administered doses (IBID). This shows that FUS-MB in combination with intravenous antibody delivery yielded more successful outcomes in AD effected models.

Research also found that IVg administration post FUS-MB treatment showed reduced tumor necrosis factor alpha (TNF-α) levels and increased neurogenesis in the hippocampus, also understood as the process for new neuron creation in the brain (Hosseini, et al. 2022). This shows that FUS can not only allow for more effective targeted drug delivery measures, but also increase the efficacy of the intended drug outcome with reduced Aβ plaque size and surface area. Relative to a patient centric approach FUS-MB could potentially produce more successful patient outcomes for those affected by AD with a more localized and controlled method at a lowered dose, which allows for adjacent tissue preservation (IBID).

LITUS can be used as another form of FUS-MB with integration of microbubbles, this allows for temporary BBBO for drug delivery similarly seen in the research focused on various FUS-MB techniques at different frequencies (Hu, et al. 2023). LITUS uses a lower intensity tactic for FUS and has also been found to enhance the delivery of anti-Aβ antibodies and other AD targeted drugs to specific brain regions (IBID). LITUS has been found to also reduce plaques through a loosened approach of the Tau protein bind, which

can result in more optimal neuronal function (IBID). Various levels of this research has been performed through the use of mouse models as effective clinical indications and protocols have not yet been established for human trials (Miller & O'Callaghan, 2017). The studies with mice have shown passive and active immune capabilities to facilitate reduction in plaques and improve cognitive functionality; however, the failed trials performed in humans may have been attributed to the inability for drugs to cross the BBB or a low antibody bind and response rate due to the aged AD individual (IBID). The advancements in FUS and FUS research have opened the door for more effective solutions to address this issue. Now that research exists and can further support the use of FUS for BBBO, new research methodologies should be established to integrate these drug treatments in combination with FUS to determine target protocols for more successful human trials.

The value this research has on the future of AD treatment and therapy can be understood as significant given no cure still remains and many of the current FDA approved medications are not able to pass through the BBB (Doke, et al. 2023). The current FDA approved medications for AD include acetylcholinesterase inhibitors, NMDA receptor antagonists, monoclonal antibody bapineuzumab, NFG gene therapy, and etanercept to prevent TNF (IBID). These approved medications are still not enough to successfully stop the progression of the disease (IBID). This further supports why more research needs to be completed to address the combination of both FUS and FDA approved medications for AD so that revolutionary treatments can be established. The gaps in drug delivery for AD have been identified and solved with FUS research and now

these methods need to be addressed in scientific studies so that AD therapies can continue to move towards more successful patient outcomes and slow the AD disease progression.

Parkinson's Disease and BBBO:

Drug treatment for PD mirrors many of the same challenges seen with AD and BBBO. These challenges make become difficult for anti-PD drugs to cross the BBB without another type of controlled force to initiate the opening. Most of the research on PD and BBBO references success that has been found in AD research and BBBO in hopes to mimic many of the same processes for successful treatment of PD with therapeutics (Gasca-Salas, et al. 2021). The ability to determine a definitive PD diagnosis has been shown to be one of the main obstacles for the treatment of PD (Chen, et al. 2023). Medical history, presenting symptoms, and family history, are the current clinical factors associated with the diagnostic process to confirm the PD pathology in patients, however, this data has not been considered sufficient enough in most cases, to provide a confirmed diagnosis (IBID). This example leverages the potential use of TCD as a plausible tool to assess the cerebral vascular functionality of patients with a possible presentation of PD.

Additionally, the assessment of conceivable biomarker identification in conjunction to TCD evaluation may help clinicians follow a patient's disease progression in earlier stages, which can result in more effective diagnosis and treatment of the disease over time. The inability to effectively diagnose the PD pathology in the early stages can hinder successful treatment intervention, and therefore, a clinician's ability to provide effective treatment directly correlates to the time taken to provide a confirmed diagnosis. There appears to be a few gaps in the diagnosis and treatment methodologies for PD,

which include accurate initial diagnosis and current research that can address BBBO for the delivery of anti-PD therapeutics. While the use of TCD for PD diagnosis has already been posed as a plausible methodology in earlier text, evidence to support how FUS, which includes FUS-MB, can be utilized for BBBO also remains of high priority (Cheng, et al. 2022). This most likely can be contributed to the fact that anti-PD drugs are the most common therapeutic currently used for management of the disease progression (IBID).

The approved anti-PD therapeutics consist of dopaminergic, anti-muscarinic, and anti-glutamatergic medications; however, these drugs only alleviate the dyskinesia symptoms and have not been shown to be effective as a stand-alone cure for the disease (Cheng, et al. 2022). Therapies in development are ones that target redox regulation, attenuation of misfolded and aggregated α-syn, and neuronal regeneration (IBID). More specifically, drug development has been focused on ways to halt or slow the degradation of dopamine neurons in the substantia nigra (Miller and O'Callaghan, 2017).

As these therapeutics continue to develop researchers will need to find importance in the identifiable ways that these drugs can be most effectively delivered for optimal patient success. Cheng et al. references a study completed in 2018 where FUS-MB was used to open the BBB in mice effected by the PD pathology (Cheng, et al. 2022). This study used FUS-MB to assist curcumin-loaded cerasomes through the BBB to assess the anti-PD effects on the mouse models (IBID). Although curcumin has been commonly understood as a traditional Chinese medicine that has shown anti-PD effects in vitro, much research at current has failed to support the same outcomes in vivo (IBID). Therefore, the positive results found in the study with FUS-MB and curcumin in mouse

models may be a hopeful step in the right direction for future research of drug delivery in PD patients. The FUS-MB and curcumin mouse study found that FUS-MB significantly increased curcumin accumulation in the left side of the mouse brain in ex vivo imaging and showed a significant increase in BBB permeability (IBID). This was then assessed in immunochemistry assays of the substantia nigra tissue, which showed an increase in the number of TH+ neurons, a dopaminergic neuron marker in the CNS (IBID). This research shows how FUS techniques can be utilized to increase BBB permeability for effective drug delivery in PD patients. The challenges that must be addressed are development of more advanced therapeutics to treat PD now that research supports the possibility of successfully opening the BBB and more research to identify appropriate FUS protocols and anatomical regions most suitable for these types of therapeutic delivery.

Immunotherapy treatments for PD have also been studied that aim to reduce the amount of extracellular α-syn and aggregation of larger clusters in animal PD models (Miller and O'Callaghan, 2017). These results have shown that immunotherapy treatment was effective in the reduction of neuronal protein accumulation and α-syn inclusions in the substantia nigra, with additional reduction in neurodegeneration of accumulated misfolded α-syn (IBID). Similarly, neurotrophic factor therapy accompanied by FUS was shown to deliver a greater amount of neurturin to the substantia nigra of the mouse brain compared to direct injection (IBID). Researchers have found that neurotrophic factors can protect and repair damaged neurons and dopamine neurons specifically, and dopamine neurons seem to respond more strongly to neurotrophic factors like GNDF and transforming growth factor-β (TGFDβ) in PD animal models (IBID). However, due to

the lack of successful outcomes in humans, more research needs to be completed on immunotherapy and neurotrophic factor treatment, as BBBO obstacles may still be a challenge. Researchers agree that for future treatment and effectiveness of immunotherapies and neurotrophic factor efficacy for PD, FUS can potentially reduce the BBBO burden that may hinder successful patient outcomes in human drug trials (IBID).

In addition to FUS-MB success in BBBO of the substantia nigra, other brain regions relative to the PD pathology have also been studied. Research suggests that BBBO of the right parieto-occipito-temporal cortex, the white matter predorsal frontal cortex, and the primary motor cortex has also been shown to be safe and effective (Gasca-Salas, et al. 2022). For PD patients that exhibit signs of dementia, Gasca-Salas and colleagues state how FUS for BBBO could potentially be used to target the regions associated with cognitive decline such as the striatum, amygdala, parieto-occipito-temporal cortex, motor striatum, and ventro-lateral substantia nigra pars (IBID). The thought for future research relative to BBBO in PD patients, could be that clinicians will target multiple brain regions simultaneously for the administration of anti-PD therapeutics (IBID). In order for this to be successful ample research needs to continue to include how forms of FUS are imperative for the success of PD drug delivery.

Overall, similar challenges of BBBO exist in PD treatment options. Even with approved therapeutics, there still remains no cure for PD (Cheng, et al. 2022). FUS provides researchers with an alternative controlled and regulated option to manipulate the opening of the BBB for more localized and effective drug delivery. As the development of PD therapeutics continues to advance, FUS should be considered as a tool to assist in

the treatment of PD given that various researchers agree the proven safety and reversibility are valid and well supported in scientific evidence (IBID).

Amyotrophic Lateral Sclerosis and BBBO:

As found with AD and PD, permeability of the BBB also remains a challenge for ALS treatment (Shen, et al. 2023). Current FDA approved medications for the treatment of ALS are Riluzole, a glutamate signal blocker, and Edavarone, a reactive oxidative species mitigator (Monsour, et al. 2022). Research shows that these current treatment methods only mildly slow the disease progression due to the inability to cross the BBB (Shen, et al. 2023). The targeted area for ALS treatment where disease progression can most commonly seen as a pathological indicator of the disease presents in the upper motor neurons and lower motor neurons (Abrahao, et al. 2019).

More specifically, the upper corticospinal motor neurons (CSMN) and lower spinal motor neurons (SMN) of the motor neuron circuitry have been studied as the degradation of these neurons leads to paralysis, respiratory failure, and death in most presentations of this disease pathology (Shen, et al. 2023). Additionally, recent data has shown early signs of cortical neuronal and glial dysfunction prior to the degeneration of spinal cord neurons in ALS rodent models (Abrahao, et al. 2019). This means that there are multiple signs of the ALS pathology that have been observed over time throughout research. There are limited FDA approved drugs on the market that target all of these signs and symptoms and remain effective in BBB drug delivery, which has resulted in limited success for the regression of the ALS disease pathology overtime. The rapid progression of this disease leaves individuals with about a 2–4-year life expectancy subsequent to the initial diagnosis (Meng and Lipsman, 2021).

Current invasive procedures that aim to target the affected regions of interest for ALS diseased individuals are targeted biotherapeutics injected directly into the brain and stereotactic implantation of autologous $CD133^+$ stem cells into the primary motor cortex (Abrahao, et al. 2019). The direct injection of biotherapeutics into the motor cortex of ALS rodents has been shown to significantly increase lifespan, while the injection of $CD133^+$ stem cells into the primary motor cortex of ALS subjects has demonstrated minimal success (IBID). Non-targeted pharmacological delivery approaches such as assisted transcellular transport, drug efflux inhibition, and diffuse BBB breakdown have also been tested, however, the unpredictability of off-target effects could not be controlled (IBID). The invasiveness and unpredictability of these potential adverse effects and outcomes stand as the main concern for these current approaches. BBBO with the use of MRgFUS and FUS-MB has been studied to determine if these methods could increase BBB permeability similarly seen in AD and PD drug delivery treatment.

The first human trial of BBBO with MRgFUS for ALS was completed by Abrahao and colleagues where a "single-arm study" was performed to investigate the BBBO in the primary motor cortex (Abrahao, et al. 2019). This study utilized the injection of microbubbles with MRgFUS at a lower frequency to mechanically disrupt the BBB and prevent permanent damage of tissue (IBID). Abrahao and colleagues had to reference various studies that had successfully used FUS to open the BBB for more effective drug delivery treatment in AD and PD due to the limited number of studies centered around FUS and ALS (IBID). This highlights a significant step forward in the right direction for more successful outcomes to slow the ALS disease progression.

The study by Abrahao and colleagues aimed to test the feasibility and safety of MRgFUS and microbubbles in subjects with ALS (Abrahao, et al. 2019). The population consisted of 4 subjects with a median age of 61 that had a confirmed diagnosis of ALS with upper motor neuron dysfunction (IBID). Results for this study showed BBBO was successful in all subjects and was confirmed from the gadolinium leakage at the FUS target (IBID). Gadolinium was administered to help identify whether or not the BBB within the primary motor cortex was penetrated from the sonication of the FUS treatment (IBID). No adverse events from the device or the procedure were found in any of the subjects' post-treatment and at the 30-day follow-up none of the patients exhibited signs of hemorrhaging, ischemia, gliosis, or worsened atrophy (IBID). The use of real-time magnetic resonance thermography, acoustic spectrum monitoring, and patient communication of symptoms allowed for more accuracy in beam sonication of the target region, tissue integrity, and adaptability to adjust in the event of any complication (IBID). These are considered features of MRgFUS that other invasive techniques cannot provide, which make this tool more patient centric as a non-invasive technique with the potential for even more successful outcomes in future studies. The results yielded a successful first human-trial despite the small population of subjects and posed as a new potential method for drug treatment delivery in ALS due to the increased access of degenerated neurons and glial cells of the primary motor cortex (IBID).

The research performed by Abrahao, et al. can be taken a step further with research completed by Shen and colleagues where they initiated a study to test the efficacy of Edarovone (Eda) drug delivery in $SOD1^{G93A}$ mouse models with FUS-MB (Shen, et al. 2023). The goal of this study was to determine if FUS-MB with the

administration of Eda to the motor cortex could positively reduce the progression of ALS (IBID). There were four sites with no overlap in the motor cortex that were targeted and again later evaluated through the use of magnetic resonance imaging and gadolinium injection (IBID). There were a few limitations to this study which include the focus of only one transgenic mouse type, the $SOD1^{G93A}$ (IBID). This specific gene mutation has been linked to roughly 20% of familial ALS cases, which may not necessarily be representative to the larger population of ALS cases (IBID). Gene mutations like TDP-43 were not included in the Shen, et al. study, but can be commonly seen in the ALS pathology and therefore should be included in future research considerations (IBID). Also, the total population of mice equated to fifty, which can be acknowledge as a decent sized population, however, the gender was only female (IBID). Overall, future research studies should include TDP-43 transgenic mouse models, male mouse models, and variations of Eda dosage to further explore how FUS can be useful in more effective drug delivery for ALS patients.

The results of the Shen and colleagues study presented data from six groups that consisted of the wild type (WT), ALS, FUS, FUS-MB, Eda, and FUS-MB+Eda (Shen, et al. 2023). The WT group was the control group; the ALS group consisted of the $SOD1^{G93A}$ ALS mouse models that were injected with saline; the FUS group was treated with sonification without microbubbles; the FUS-MB was treated with sonification and microbubbles; the Eda group was treated with Eda medication only; and the FUS-MB+Eda was treated with FUS-MB and the administration of Eda (IBID). The differences between these groups should be acknowledged as the data was evaluated for all the groups and various groups showed statistically significant differences in the

results. This becomes imperative to understand for further analysis relative to the effectiveness of the study.

The focal point of analysis from the data collected was centered around BBBO effectiveness, status of gait parameters and gastrocnemius muscle atrophy, neuroprotection of CSMN and SMN, neuroinflammation response to microglial activation and astrocytosis, and level of misfolded SOD1 accumulation in $SOD1^{G93A}$ mice (Shen, et al. 2023). The results showed that the FUS-MB+Eda yielded a two-fold increase in the uptake of Eda into the motor cortices compared to the Eda only group (IBID). Relative to gait parameters, the ALS group demonstrated significant gait abnormalities like stride length, stance time, and average speed compared to the WT group, which validates that gait disturbances are a sign of the ALS pathology. Additionally, there were no significant gait differences in the FUS and FUS-MB group compared to the ALS group, this shows that the potential neuromodulation technique with FUS or FUS-MB to treat gait abnormalities in ALS patients may not be as effective at the frequency used for this specific study. The four gait parameters significantly improved in both the Eda only and FUS-MB+Eda groups (IBID).

In response to gastrocnemius muscle atrophy, the FUS-MB+Eda group significantly delayed muscle atrophy by 13.9% compared to the Eda only group (Shen, et al. 2023). Between the WT and ALS group, the CSMN in the WT group were 51.1% larger in size compared to the ALS group (IBID). Similarly, Eda treatment significantly improved CSMN sizes compared to the ALS group and a slower rate of CSMN atrophy was seen in the FUS-MB+Eda group compared to both the ALS and Eda group (IBID). Relative to SMNs, ALS mice showed a 70.2% total loss compared to the WT group,

whereas FUS-MB+Eda increased the number of SMNs by 25.2% compared to the Eda group alone (IBID). This shows that FUS-MB with the administration of an ALS approved drug has the potential to serve as a neuroprotectant and increase motor neuron regeneration.

Continued results showed the abnormal morphology of microglia was highly apparent in the ventral horn of the lumbar spinal cord in ALS, FUS, and FUS-MB groups compared to the FUS-MB+Eda group that presented with microglia morphological recovery and improvement in astrocytosis (Shen, et al. 2023). This again illustrates how the use of FUS or FUS-MB alone to modify neuroinflammation may not be as effective at the specific frequency in which this study used FUS, or without the addition of a therapeutic agent, given that a similar response was seen in the ALS group. Lastly, the amount of misfolded SOD1 accumulation in the motor cortex of $SOD1^{G93A}$ mouse models was reduced in the FUS-MB+Eda group without a significant difference to that of the WT group (IBID). In essence, the FUS-MB+Eda group showed more reliable improvement in reduction of misfolded SOD1 protein in the $SOD1^{G93A}$ mice (IBID).

The numerous conclusions drawn in the Shen, et al. study highlight important characteristics about the ALS disease pathology and the use of FUS for more effective treatment methods, which has opened the door for a more focused approach to future ALS studies. Abrahao, et al. and Shen, et al. are some of the few to dive deeper into the use of FUS for more effective ALS treatment and drug delivery and their findings have placed researchers in a position to continue the success of this research. This disease can be debilitating and present with a short life expectancy, however, the current research has

gained significant traction that can point investigators towards a more humanistic approach for the treatment of neurodegenerative diseases like ALS.

PART THREE

Medical and Health Humanities Lens: Quality of Life Analysis

Quality of Life and Neurodegenerative Diseases:

Neurodegenerative diseases can be debilitating diseases that can significantly impact a patient's overall quality of life. These types of diseases can impact the daily lives of individuals and can affect professional, social, and familial relationships which makes these diseases one of the most focal medical and socioeconomic problems of this time (Batista and Pereira, 2016). As previously outlined in earlier sections, the main issue with neurodegenerative diseases remains centered around the fact that diagnoses are typically confirmed later in the disease pathology directly, which can affect one's ability to integrate advantageous treatment interventions (IBID). A commonly used measurement to assess quality of life in patients can be referred to as the Health-Related Quality of Life (HRQoL) scale aimed to evaluate physical, psychological, and social scopes on the impact of the disease (IBID).

There are other instruments that have also been established for quality-of-life measurement; however, most of these tools aim to assess similar components relative to an individual's daily life. Due to these impedances, individuals with neurodegenerative diseases tend to see a loss of independence and ultimately become reliant on the care and support of others to continue daily acts of living (Aza, et al. 2022). Dementia, which can be considered a common effect of neurodegenerative diseases given the progressive deterioration of vital neuronal function over time (IBID). Dementia has been shown to affect 50 million people with some type of neurodegenerative disease globally (IBID).

In addition to the quality-of-life metrics negatively impacted in individuals with neurodegenerative diseases, family and caregivers that provide care or support these individuals are also negatively affected (Aza, et al. 2022). In some instances, positive effects can be a result of adequate care provided for someone with a neurodegenerative disease as this forces a closeness with the affected person, however, depression, anxiety, stress, and burnout can also be a result of these difficult situations (IBID). Similar to the HRQoL scale, another scale that measures how families or persons heavily integrated in the care of individuals with neurodegenerative diseases are affected, can be referred to as the Family Quality of Life (FQoL) metrics (IBID). This scale utilizes objective and subjective indicators to determine strengths and challenges seen amongst caregivers that support individuals with these debilitating diseases (IBID). FQoL metrics should reside at optimal levels for patients with neurodegenerative diseases, as these metrics often represent the point of initiation to build a support plan, which can also influence future improvement of professional attention, services, policies, and state, regional, and local agendas (IBID).

The FQoL scale has the potential to incorporate both quantitative and qualitative measurements from families and caregivers; however, research has shown that many models do not necessarily use a mixed methods approach (Aza, et al. 2022). Without qualitative data there would appear to be no baseline for the acquisition of quantitative results, which means that for both HRQoL metrics relative to individuals with neurodegenerative diseases and FQoL measurements for caregivers, these tools may be more valuable if they also included qualitative analyses to further support the data on

how quality of life can be affected in both patients and caregivers associated with neurodegenerative diseases.

The value of quality-of-life observation in both caregivers and affected patients with neurodegenerative diseases, allows for a push on clinical advancements to reduce these burdens and increase quality of life through the adoption of advanced diagnostic tools for earlier diagnosis, which can then lead to earlier treatment intervention, preferably with technology that intervenes from a less invasive approach. If researchers can develop ways to diagnosis a pathology earlier on in the disease process, patients can start treatment plans earlier, which can hopefully reduce or slow the progression of the disease and can potentially result in increased quality of life scores for both patients and caregivers. However, the use of quantitative and qualitative analyses must be considered to provide a more wholesome perspective of the entire disease process, as the clinical and scientific progressions are just one component on the affected individuals. If the clinical and scientific components are the only part of the disease process that are considered, then this leaves out the humanistic perspective of how these debilitating diseases affect patients and caregivers, which can leave only a partial consideration of care. These quality-of-life outcomes may have the ability to contribute to the clinical and scientific discoveries of the disease, as the lived person's perspective from a quantitative and qualitative point of view have the potential to provide insight into the affected person's disease state.

Alzheimer's Disease:

Currently no identified cure for AD exists and much of the current treatment remains centered around maintenance on a patient's quality of life (Barbe, et al. 2018).

The hopeful addition of new approaches for earlier diagnostic assessment and treatment intervention may soon allow for the expansion of the entire care regimen. There are limited current studies that solely focus on quality-of-life measurement in patients with AD, which could be a result of the implementation of new advancements aimed to improve quality of life from a patient centric point of view that have yet to be assessed. These advancements can be understood as potential early diagnostic tools like TCD and biomarkers that aim to confirm a pathology at the onset of the disease, or even the forward progression of focused ultrasound as a treatment modality for neuromodulation techniques including BBBO for earlier drug delivery.

A possible reason for limited studies could be that the main focus of AD research remains centered around the discovery of a cure or ways to slow the progression of the disease rather than just the maintenance on a patient's quality of life from a more palliative care perspective. Although this concept may be optimistic, quality of life still can be identified as an important factor for consideration, as these diseases tend to progress quickly. Quality of life research that has been established for patients with AD can be considered central to the management of medical, cognitive, psychological, social, and functional effects of the disease (Barbe, et al. 2018). The HRQoL scale has been seen as an important tool for the assessment of many of these indicators precisely because this tool appears to be subjective to a patient's own experiences (IBID). More specifically for AD, an assessment tool Quality of Life in Alzheimer Disease (QoL-AD) may also be used, which incorporates intel from both the patient's point of view as well as the caregiver's perspective of the patient's HRQoL (IBID).

One study looked at the HRQoL from patients with AD and the correlated scores from the caregiver's perspective, measured with the QoL-AD scale (Barbe, et al. 2018). In this study, depression and polypharmacy, where one takes more than three drugs to treat for other comorbidities, were found to be associated with the QoL-AD for both patient and caregiver scores (IBID). This shows that depressive behavior was observed by both patients and caregivers due to the impact treatment for multiple comorbidities had on patients' perception of physical health (IBID). Depression has been shown to be a common comorbidity for individuals with AD, which makes the treatment for depression imperative to manage quality of life levels (IBID). Despite the commonness of depression amongst individuals with AD, depression has been shown to be difficult to treat as many mistake this disorder for dementia, which presents with apathy and or decreased energy levels (IBID). In addition to the treatment of these depressive symptoms in individuals with AD, a risk remains that the treatment of depression may counteract with the effects of other drugs prescribed to treat underlying comorbidities (IBID). This concept makes management of a patient's quality of life difficult for clinicians because of the many factors associated with the disease.

The study by Barbe, et al. also focused on the effects of polypharmacy on patient and caregiver scores of the QoL-AD (Barbe, et al. 2018). The study found that both the caregiver's perception and the patient's perception on the effects of polypharmacy was shown to be poor (IBID). Researchers suggest that the patient's perceived health status due to the treatment of many health factors can affect the view of their current state of well-being, which can show a decline in the QoL-AD scores (IBID). Similarly, when

caregivers must see their loved ones suffer from many different comorbidities, this can provoke them to rate the QoL-AD more negatively (IBID).

Another noteworthy conclusion in the Barbe and colleagues' study was that anxiety was shown to be evaluated at a lower QoL-AD score from the patient's perspective, but not similarly reflected from the caregiver's (Barbe, et al. 2018). This could have been a result of an overlap in representation of depression and anxiety symptoms, which could have affected the caregiver's ability to properly distinguish a difference between the two (IBID). Comparable to depression, anxiety can also be treated with medication and may be a psychological factor that should be considered for treatment and improvement of HRQoL scores (IBID). The difference between data for anxiety specifically can be of interest because this data shows how the patient perceived these symptoms as relevant and the caregiver did not provide as much acknowledgement. This can show that anxiety for individuals with AD may present with more internal vs. external symptoms and thus would be difficult for someone other than the patient to observe or identify. These observations further support how the acknowledgement of these quantitative results translate into qualitative support, as the qualitative observations from the patient with AD may be helpful to provide insight on the disease progression to not only caregivers, but clinicians as well.

Caregiver burden was also seen to be significantly associated with the caregiver's score on the QoL-AD most likely due to the fact that caregivers bear the burden of care for the individuals with AD, which can directly affect the caregiver's quality of care as the disease progresses (Barbe, et al. 2018). The caregiver burden was reported relative to energy, mood, memory, family, marriage, friends, ability to do chores, ability to do things

for fun, and life as a whole (IBID). All of these factors where caregiver burden was reported by the caregiver relative to the effects on the patient may be because the caregiver has to assume the role for proper maintenance of all of these areas not only for themselves, but for the individual affected by AD due to the progression of the disease (IBID). As the disease progresses for AD patients, many of these daily associations become more difficult to maintain which places more weight on the shoulders of the caregiver to carry and maintain. This in turn leads to the inquiry on how the caregiver's HRQoL may be directly affected as they typically become the primary supporter for individuals with these debilitating diseases.

Vellone, et al. performed a qualitative study in Italy that focused on quality-of-life responses from caregivers on their own subjective emotions towards their experience of care for a loved one with AD found that when caregivers were asked to describe what quality of life meant, many of them chose words that were associated with psychological well-being and freedom (Vellone, et al. 2008). Researchers found this to be insightful as these were descriptive characteristics of qualities they no longer had after their time became dedicated to the care and suppor of their loved one with AD (IBID). The value of these qualitative observations gives keen insight into the mindsets of these caregivers, which allows one to question how their emotions can directly affect the care of those with AD. Care for oneself and maintenance of optimal health as a caregiver was viewed as impossible after these individuals took on the burden of care for the individuals with AD (IBID).

Moreover, caregivers reported that increased health of the patient, independence from them, and more help with the ability to provide proper care could help to improve

their quality-of-life score (Vellone, et al. 2008). This shows that the dependence AD individuals have on their caregivers effects the quality of life of these caregivers, which makes these burdens extremely difficult to carry. This data provides valued importance for researchers, so that they can continue to explore earlier diagnostic methods such as TCD and biomarkers, to confirm the AD pathology earlier on for more immediate treatment intervention for patients. Additionally, minimally invasive treatment options such as FUS also need to be continuously studied as these therapeutic techniques may help to slow the progression of the disease, which can reduce the burden on caregivers and ultimately help to improve the quality of life in both patients and caregivers. If implementation of early diagnostic and treatment modalities that are non-invasive and inexpensive, can not only slow the progression of the disease, but help to maintain a sense of independence for individuals with AD, with the addition of maintenance relative to the quality of life for both parties, then this would appear to be foolish not to focus efforts on the advancements these modalities.

Parkinson's Disease:

PD can be commonly referred to as neurodegenerative disease that affects motor, cognitive, and autonomic function that leaves patients in a debilitated state (Duvdevani, et al. 2024). The mental and physical disabilities that individuals with PD experience can present in a multitude of ways, which can make the effect on quality of life substantial (Chekani, et al. 2016). One study assessed how quality of life was affected in patients with PD and dementia and focused on the physical component summary (PCS) and the mental component summary (MCS) (IBID). This was a national survey that collected data over the course of 9 years (IBID). The results of this study showed that patients with

PD had lower PCS scores compared to those with dementia, which could possibly be attributed to the fact that PD presents as a movement disorder that can result in reduced motor functionin due to symptoms like bradykinesia, rigidity, rest tremor, and postural imbalances (IBID). Although these symptoms can significantly impact the quality of life of PD patients, this study showed that there was no significant difference between patients that sought out help for the completion of daily activities compared to the dementia group (IBID). Researchers suggest that this may be due to the fact that patients with PD may try to compensate with other avenues to maintain their autonomy (IBID). This perspective can be of interest because it shows that the motor function degeneration of PD may be more exhaustive than cognitive degeneration and allow PD individuals to still recognize their autonomy and aim to find other avenues to compensate for the lack of motor function.

There are many variations of how PD can present, so this conclusion may be a limitation as this has been strictly drawn from the study performed by Chekani, et al., however, in the quality of life metrics for AD, these individuals found acceptance of their independence difficult as their independence was no longer attainable as the disease continued to progress, which may have placed them in more of a depressive and helpless state (Barbe, et al. 2018 & Chekani, et al. 2016). This observation may actually provide a more thorough consideration on how the disease progresses from a cognitive and behavioral perspective relative to the diseased individual's point of view. Again, this places emphasis on how the lived person's experience affected by these types of crippling neurodegenerative diseases may actually help researchers to better understand the disease progression overtime from a scientific approach.

The question may be posed relationally to how one may link the qualitative data for PD to the scientific attributes of the disease pathology. Various research studies support the concept that the main pathological shifts in PD are due to a significant loss in dopaminergic neurons in the substantia nigra, which affects motor response and skills (Hu, et al. 2023 & Zhang, et al. 2021). This may be the exact reason why neuromodulation methods that use FUS, aim to target these regions in a non-invasive way to help slow the disease progression and improve motor function in PD patients (Hu, et al. 2023). A similar observation can be seen in the quality of life analysis which shows how PD patients had lower PCS scores compared to those with dementia, but were not statistically different compared to dementia patients on the basis of help for daily activities, which allows one to infer that the cognitive recognition of one's own autonomy with PD still existed with an core desire or motivation (Chekani, et al. 2016). This could imply that cognitive deficits seen in other neurodegenerative diseases may not necessarily be as relative to the quality-of-life scores with PD patients, which shows researchers and clinicians that the motor effects of the disease pathology may be the main factor that affects quality of life outcomes in PD patients. Therefore, if the treatment focus remains set on the attainment of increased motor movement capabilities, this may have the ability to indirectly increase quality of life scores and slow the progression of the disease with more manageable maintenance tactics.

This hypothesis can also be supported by a systematic review of factors that affect a PD patient's quality of life, where Zhao and colleagues found that the anxiety and depression effects on quality of life appeared to be contradictory because some studies showed evidence that supported that hypothesis and other studies did not find a

significant difference between PD individuals and healthy controls (Zhao, et al. 2021). This shows that the common factor amongst various studies may be relative to motor deficits and capabilities and how they can affect the quality of life of patients with PD (Chekani, et al. 2016 & Zhao, et al. 2021). This does not mean that cognitive deficits do not affect patients with PD, but rather poses that maybe motor deficits are the most exhaustive and affect quality of life more in depth.

As similarly outlined in the AD quality of life section, caregiver quality of life has also been viewed as an important measurement to understand for the overall quality of life of patients that live with a neurodegenerative disease. Research has supported that those with PD have a longer life expectancy due to improvements in diagnostic accuracy and drugs that control symptoms like Levodopa (Nagaki, et al. 2023). However, even with a drug that helps to control symptoms, the long-term use can cause side effects like dyskinesia and potentially even wear off or completely decline in effectiveness (IBID). This places emphasis on how the use of FUS as a treatment modality can not only help to improve motor function in patients with PD, but also with the information from Nagaki, et al. one can see how this may also help to increase PD patients and their caregiver's quality of life (IBID). The inability for Levodopa to work long-term places a burden on PD caregivers as they will then be required to make up in care for what the drug cannot control. This also places emphasis on how caregiver quality of life can subsequently impact the patient's quality of life, as the caregiver burden can result in poorer quality of care for the PD patient (IBID).

A systematic review by Perepezko, et al. looked at 32 different articles relative to caregiver's quality of life with PD individuals (Perpezko, et al. 2023). The common

themes that emerged amongst these various studies were burden, strain, quality of life and satisfaction, demographic factors, psychological factors, relationship factors, and caregiver input (IBID). This systematic review showed that about 90% of the articles showed an association between caregiver burden and the quality of life of PD patients (IBID). Additionally, a decreased quality of life score for the caregiver was associated with a low quality of life score for the PD patient (IBID). This demonstrates the association between quality of life for the caregiver and patient and how the quality of life for the caregiver may directly affect the quality of life for the PD patient.

These discoveries are relevant because the longer the adoption may take for earlier diagnostic techniques and treatment for PD patients, the more burden and strain this can cause on the caregivers, which creates a cycle of continued illness from a mental, emotional, and behavioral perspective. Care for an individual with a neurodegenerative disease does not only require increased attention over time, but the mental, emotional, and psychological effects this can have for loved ones that watch these individuals decline can also be troublesome. The lack of standardization in not only diagnostic methods and treatment approaches, but also continuum of care management for caregivers can affect more than just the diseased individual. Further research needs to be assessed from a whole person point of view for PD, where diagnostic, treatment, and care management protocols are established to create the most optimal outcomes for those that suffer from PD and those that take on the burden of the disease as a caregiver throughout the patient's journey of debilitation.

Amyotrophic Lateral Sclerosis:

The prevalence of ALS appears to be about 5.2-7.9 people per 100,000 within the United States (Kvam, et al. 2023). Many patients with ALS suffer from symptoms like arm and leg weakness, speech, inability to properly swallow and respiratory dysfunction, as well as cognitive and behavioral impairments (IBID). There are limited treatment options available for patients with ALS, which means quality of life and quality of care are important factors of consideration relative to quantifiable humanistic measures for patients with ALS (IBID). Some of the common ways that quality of life can be assessed in patients with ALS exists through the ALS Functional Rating Scale (ALSFRS) and the ALS Specific Quality of Life Instrument (ALSSQOL) (Simmons, 2015). A unit of measurement remains important for quantification for how quality of life and care affect patients and caregivers throughout the disease process. This remains especially true for neurodegenerative diseases where there may be limited treatment options to help slow the progression of the disease.

Aside from progressive limb weakness on quality of life, ALS psychological symptoms like depression, hopelessness, and anxiety can also affect a patients' quality of life (IBID). Quality of life research supports that these factors are important in the ALS clinical assessment, as they can directly affect quality of life, even if these factors are not a common measurement for research outcomes (Simmons, 2015). On average the psychological health of patients with ALS has shown to be lower compared to the general population (IBID). This makes sense because the disease influences an individual's ability to perform daily tasks overtime, which includes tasks that they may once have been able to do with confidence and independence.

Due to the average age for the onset of ALS, people that suffer from this neurodegenerative disease may more than likely have lived out a majority of their life without the dependence on another individual unless they suffered from other underlying comorbidities. Independence can be referred to as a state of autonomy that many humans strive for even at a young age. The idea of "growing up" can insinuate a sense of self-reliance that one may hope to acquire as they age, which can possibly even release the need and desire to be fully dependent on the individuals that helped raise them. When that sense of independence happens to be removed as a result of a debilitating disease, this in turn may affect the autonomy one has over their own body. Additionally, the loss of autonomy can potentially lead to poorer psychological health as the reliance on others becomes the only way to function. This could be why psychological health does not always decline when strength and motor function decline in ALS patients because those patients may still have function that gives them a sense of their own autonomy (Simmons, 2015). When those motor skills and cognitive skills decline so much that the patient becomes no longer able to complete tasks on their own, could be when clinicians may start to see a decline in mental health, which may be directly correlated to the progression rate of the disease.

One study outlined that about 10% of patients with ALS meet the criteria for depression and on average 41.3% of ALS patients exhibited medium levels of anxiety (Simmons, 2015). These percentages seem relatively low compared to the decline in motor functionality of the disease and could be potentially related to the fact that areas of cognitive decline that can impact psychological health in ALS patients typically present with personality changes, irritability, obsessions, and poor insight rather than memory

loss or dementia seen in about 20% of ALS individuals (Simmons, 2015; Phukan, et al. 2007; Yancey, 2020).

This could mean that psychological symptoms ALS patients experience may not necessarily be a result of the disease, but more so a result of how the disease affects them at that time in the disease process. Additionally, the higher rate of anxiety seen in ALS individuals may be contributed to the pain that ALS patients suffer from like muscle cramps, spasticity, and immobility (Simmons, 2015). Pain was reported in at least 50% of patients in one study and some researchers have found that pain and quality of life were correlated with one another (IBID). This data shows that quality of life reports relative to these factors can affect a patient's quality of life and quality of care. Whether this be strictly lack of motor functionality that affects a patient's ability to do tasks independently or the combination of lack of motor functionality and the effect on one's emotions towards their own autonomy that presents as a decline in psychological health, these factors must be considered by clinicians for the determination of the most optimal intervention and care management plan (IBID). Since this disease does not have a cure, quality of life data remains imperative for clinicians to understand as this can help them practice from a patient centric care approach, while they wait for more research to be completed on treatment interventions like FUS for BBBO and earlier drug treatment delivery.

In addition to the patient's quality of life post-ALS diagnosis, the impact on quality of life for caregivers also remains important to understand. Caregivers are often faced with physical, emotional, and social challenges when they care for patients with ALS (Larsson, et al. 2022). As the disease progresses, the caregiver's intervention

becomes more focused on the care of the patient, which can affect other areas of the caregiver's life that may contribute to their overall quality of life (IBID). One study looked at individual quality of life (iQoL) in relatives of patients with ALS from diagnosis throughout the disease progression and also aimed to determine how iQoL correlated with the ALS patients' physical function and relatives' psychological health (IBID). This study used quantitative and qualitative measures to determine outcomes (IBID).

The conclusions of this study showed that family, friends, health, and leisure were the top nominated areas that relatives felt impacted their quality of life in that moment in time relative to the state in the disease progression from diagnosis (Larsson, et al. 2022). One noteworthy point was that among the 5 group of relatives: a) 1-3 months post-diagnosis, b) after 6 months, c) after 12 months, d) after 18 months, and e) after 24 months, the cue level score for how one's own health was affected with 1 being the worst and 7 being the best, the scores actually increased from group a to group e (IBID). This trend stands as an important point to identify because this data allows one to question, if research supports that the disease progression can have a negative impact on the caregivers iQoL, then why would their perspective of their own health be rated higher in groups that cared for an ALS patient in a longer timeframe? Additionally, why would the qualitative response of these individuals show that they expressed a lack of time for oneself with descriptive words such as worries, stress, the burden of caring, and lack of relaxation to think about their situation, but rated a cue level that signified these functional areas presented as adequate (IBID)?

Perhaps, this may come down to acceptance of the disease state overtime, that relatives and caregivers at some point from diagnosis throughout the disease progression were able accept the state that their loved one was in, but would still describe the situation from a qualitative perspective as worse than the cue level. This provokes in depth thought because these answers demonstrate how qualitative and quantitative outcomes can elicit a different response amongst people and poses the question as to which response holds more weight in relation to the relatives' and caregivers' quality of life. Could this be that when asked to respond to a score on a quality-of-life scale individuals may have cognitively felt that they accepted the state their loved one was in enough to take their own life back and focus on their health? Or could the response be related to the fact that these caregivers had to witness someone with a debilitating disease, which inclined them to prioritize their own health throughout the disease progression, yet still made them want to describe this process as burdensome? Or possibly even that on a evaluation scale the caregiver felt that their own health compared to their loved one with ALS as the disease had progressed was nowhere near comparable to the state their loved one was in and thus prompted them to shift their own health outlook to something more positive?

These are all questions that researchers may need to explore further as the own health trend lacks supportive qualitative evidence to correlate how a subjective descriptive response from the caregiver almost appears opposite to the assessment score based on the length of care time for an ALS individual post-diagnosis. This does not mean that the conclusions drawn are not necessarily accurate, but simply questions the contradictory responses to one another and questions what the motive could be for

differentiation. The study supports this argument with highlights in the limitations section, which showed that the researchers did not use a weighted procedure to weight the cues, which could have ultimately influenced the amount of effort the respondent used to answer those types of ratings honestly (IBID).

Overall data supports that caregivers' quality of life can be affected throughout the ALS disease progression, however, to what extent, needs to be explored further. Anxiety as a psychological factor was apparent as this disorder did affect all 5 groups and showed that there may be a correlation with emotional well-being of caregivers throughout the disease trajectory (Larsson, et al. 2022). More research needs to be done to determine how ALS affects the quality of life of not only caregivers, but patients as well because there are limited studies that truly dive into this relationship. Researchers need to continue to identify these gaps in quality-of-life analyses of ALS patients and their caregivers because as of current no cure remains. If researchers and clinicians can work together to identify the most appropriate care management plan in relation to quality of life and new treatment advancements like FUS, these individuals may be able to reduce the quality-of-life burden that currently exists for both patients and caregivers. Furthermore, if an earlier diagnosis of ALS can be confirmed using multidimensional diagnostic approaches that include the potential use of TCD, then this cascade of events post-diagnosis into disease progression may have the ability to be significantly reduced over time for both patients and caregivers.

Economic Burden of Neurodegenerative Diseases: Cost-Benefit Analysis

Statistics from The World Health Organization (WHO) and United Nations (UN) show that by 2050 the age group of individuals 60 years and older will increase from less

than 1 million as of 2020, to a population size of about 2 million (Maresova, et al. 2020). The shifts in demographics over time can results in changes from an economic and social perspective (IBID). For example, cases of dementia which exceeds over 50 million cases, often requires a caregiver to dedicate their time, efforts, and money to accommodate these types of individuals that are limited in the performance of daily activities as they tend to become fully dependent on their caregivers (IBID). In about 80% of cases caregivers are relatives (IBID). Studies have estimated that caregivers dedicate about 47 hours per week to care for their affected family member (IBID). One can infer that if an average work week consists of about 40 hours for typical salaried employees, and these caregivers dedicate 47 hours each week to someone with dementia as a result of a neurodegenerative disease, then those caregivers would most likely need to quit their jobs as they may not have time to work full-time. As result of the caregiver separation from their main source of income to care for an affected individual, one can ultimately assume that this would cause economic tension and strain.

This economic burden may essentially affect the quality of life for both the affected individual and the caregiver as most governments do not acknowledge how these issues affect quality of life and therefore have limited resources available to help caregivers and patients throughout the debilitating disease journey (IBID). Despite the limited resources available, there has been an estimated global and societal cost of dementia, which equates to about $818 billion in 2015 (IBID). One would think that these numbers would be enough for an increase in implementation of care management processes for patients and caregivers, but because the focus would be centered around

quality-of-life increase and not solely concentrated on medical or research directions, these critical demands appear to fall behind in rank relative to patient care.

Dementia remains apparent in various forms of AD, PD, and ALS. The most frequently diagnosed form of dementia happens as a result of AD and affects about 5% of individuals at the age of 65 and half of the population of individuals at the age of 85 (Maresova, et al. 2020). Mild cognitive impairment can be seen in early stages of PD and typically progresses into dementia for about 80% of those affected patients in the later stages of the disease (IBID). The dementia seen in ALS patients may not necessarily present as cognitive impairment, but rather upper and lower motor neuron impairment that eventually leads to complex paralysis of the entire body (IBID). Regardless of the dementia presentation, these diseases essentially at some point require full dependence on someone else to care for these individuals affected by neurodegenerative diseases. This results in a need for complex care from a psychological, social, economic, and biomedical perspective.

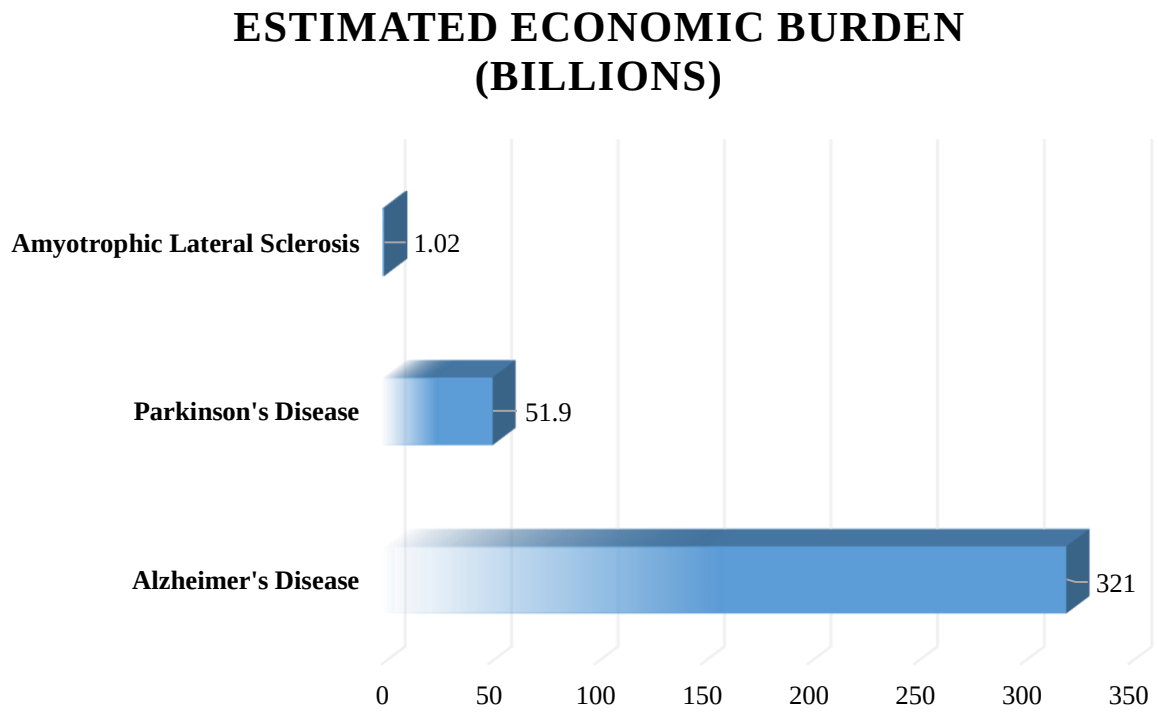
The need for earlier diagnostic techniques becomes crucial in the determination of the most optimal treatment plan for these affected patients, but without an effective treatment method, early diagnostic techniques serve minimal value. In order to address how quality of life in patients and caregivers affected by AD, PD, and ALS can be improved, researchers and clinicians must determine ways to bridge the gap between diagnosis and treatment through integrative approaches of more advanced diagnostic and treatment techniques like TCD and FUS, that may help to slow the progression of the disease earlier on in the patient's journey.

Estimated Economic Costs of Neurodegenerative Diseases:

The estimated economic costs for AD, PD, and ALS varies based upon the year the data was collected, however, the most current values range from 2017-2022 respectively (Skaria, et al. 2022; Yang, et al. 2020; Berry, et al. 2023). Figure 1 exemplifies these findings supported by the various researchers cited above (IBID).

Figure 1

Systematic Review of Estimated Economic Burden for the Associated Neurodegenerative Diseases



Note. The estimated economic burden of Alzheimer's Disease, Parkinson's Disease, and Amyotrophic Lateral Sclerosis from data published between 2017-2022 with some that include both direct and indirect costs. Data generated with information from *The economic and societal burden of Alzheimer disease: managed care considerations* (pg 1), by Skaria, A. P. 2022, *The American Journal of Managed Care*, *28*(10 Suppl), S188-S196; *Current and projected future economic burden of Parkinson's disease in the US* (pg. 1), by Yang, et al. 2020, *npj Parkinson's Disease*, *6*(1), 15; *Epidemiology and economic burden of amyotrophic lateral sclerosis in the United States: A literature review* (pg. 445), by Berry, et al. 2023, *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 1-13.

The data from Figure 1 illustrates the estimated costs for AD, PD, and ALS (Skaria, et al. 2022; Yang, et al. 2020; Berry, et al. 2023). These costs are represented in billions with AD showing the highest costs compared to PD and ALS (IBID). Limited data remains for AD, PD, and ALS that showcase the economic costs for the exact same year and this explains why the range stems from 2017-2022. Values were represented with data from the affiliated researchers and their associated publications for data extraction purposes (IBID). PD and ALS include direct and indirect costs in the total, whereas the AD estimated costs only signify the direct costs associated with care (IBID). Skaria, et al. highlights that the values for AD may actually be higher as the indirect costs were not included in this estimated total cost (Skaria, et al. 2022).

Limited data exists that breaks down direct vs. indirect cost-of-care projections for these neurodegenerative diseases as of current, so the data that has been sourced, must be analyzed with the caveat that the AD estimated cost representation could most likely be subject to change given that this data does not include the indirect costs associated with AD treatment and care (Skaria, et al. 2022). Regardless of the estimated cost, each neurodegenerative disease listed exceeds over $1 billion in estimated costs, which presents as a significant amount especially for diseases like ALS, where the estimated prevalence stands at about 5.2-7.9 per 100,000 population (Berry, et al. 2023 & Kvam, et al. 2023). This shows that the estimated costs associated with these diseases are significant enough to consider other alternative more cost-effective and quality of life centric diagnostic and treatment modalities like TCD and FUS.

Additionally, the average onset for a majority of these neurodegenerative diseases ranges between 60-65+ years of age (Maresova, et al. 2020). This means that the patients

who experience onset at 65+ years of age are typically under Medicare, which means that the estimated costs are essentially funded by governmental healthcare programs, not private healthcare insurers. This places these high value costs for treatment and care on governmental funds, without the inclusion of associated costs to caregivers as a result of them positioned as the sole caretaker for an individual affected by a neurodegenerative disease. This relates back to the point on how there are a lack of quality-of-life processes in place for caregivers and patients related to these diseases because governments worldwide do not fully realize the scope of these issues, yet the governments are the ones, at least in the United States, highly impacted by these neurodegenerative diseases from an economic perspective (IBID).

However, despite the high costs associated with these diseases, the question remains: if there seemingly remains no cure; outlined evidence that supports limited initiative to implement quality of life care management processes for caregivers and patients; and inadequate ways to diagnose these diseases earlier on, then why are costs so high (Maresova, et al. 2020; Cheng, et al. 2022; Hu, et al. 2023; Hosseini, et al. 2022; Baldacci, et al. 2020)? What causes these direct costs that one could infer are at least somewhat covered by Medicare for the aged population of 65+ years to be economically burdensome? One possibility could be that because there are limited effective early diagnostic techniques, physicians may be required to utilize more extensive resources to try and confirm the specific neurodegenerative disease.

Additionally, if this were to be true, one can infer that there might be a delay in treatment due to the extended length of symptom presentation from the onset of symptoms to a confirmed diagnosis. Furthermore, if this delay happens to be prominent

in most of these cases, then that would also mean that there could be a delay from the initial onset of symptoms to treatment intervention. If physicians cannot confirm a diagnosis, how are they going to treat for that diagnosis?

This presents an even stronger argument for why researchers and clinicians need to standardize more effective diagnostic and treatment modalities for these patients because the cost impact on governmental programs remains evident, why those costs remain high would need to be further investigated. However, at least these conclusions would pose as an entry point for stronger initiatives relative to earlier integration of more effective diagnostic and treatment modalities for patients with neurodegenerative diseases. This in turn would allow for further advancements in the diagnosis and treatment of these diseases, which additionally can assist in the increase of patient and caregiver quality of life as a result of a slower disease progression or more manageable symptoms overtime. A case-study analysis of patient outcomes with current and proposed diagnostic and treatment modalities must be assessed to further understand how these tools can be utilized to better manage care and reduce costs.

Patient Outcomes: Case Study Analysis

Alzheimer's Disease:

Post-mortem assessment of AD patients typically has shown patterns of α-syn and TDP-43 depositions, as well as various degrees of cerebrovascular disease, which include cerebral amyloid angiopathy (Baldacci, et al. 2020). The main concept to keep in mind relative to these assessments remains centered around the fact that they have been performed post-mortem. This reiterates the lack of current standardized assessment tools utilized to identify the status of cerebrovascular disease and other vascular issues in AD

patients while they are alive prior to the onset of the disease. There are ways to utilize assessment tools like TCD to determine blood flow in patients with AD, but a standardized approach has yet to be established. Cerebral amyloid angiopathy can be identified as the main cause of lobar hemorrhage and has been studied in post-mortem reports (IBID). These studies have shown that cerebral amyloid angiography was found to be present in 20-40% of non-demented individuals, 50-60% in elderly individuals with dementia, which co-occurs at about 85-95% with AD (IBID). This data shows how cerebral vascular issues have been shown to be present in patients with AD post-mortem and could be indicative of vascular function throughout their lifetime.

Roher and colleagues found in neuropathologically confirmed AD subjects, that atherosclerotic stenosis of the cerebral arteries was greater relative to number and severity compared to non-demented controls (Roher, et al. 2011). Additionally, pulsatility index measurements and mean velocity flow of specific arteries were found to be significantly different between both the non-demented control group and the AD group (IBID). This data provides evidence that supports how TCD can be used in patients with AD at current to assess cerebral artery and other vascular functionality relative to the disease state. These discoveries may not consecrate this mechanism as a way to confirm the diagnosis without other assessment modalities, but this tool may be able to provide further insight on whether or not individuals with cardiovascular conditions that preexist are at risk for future neurodegenerative disease development. These studies can support the use of TCD as a way to monitor patients with conditions that preexist relative to cardiovascular health, so that clinicians can follow an individual's disease state prior to the potential development of a neurodegenerative disease like AD, or even be able to

administer therapeutic treatment methods to prevent the future accumulation of cerebrovascular issues.

A case study performed by Xu and colleagues aimed to investigate whether the pulsatility index of TCD could be utilized as a predictive indicator relative to the invasive assessment tool of fractional pressure ratio (Xu, et al. 2024). Fractional pressure ratio for this study measured the pressure both distal and proximal to stenotic lesion (IBID). The stenotic lesion can be understood as a passageway that has become narrowed and prevents optimal blood flow (IBID). This case study assessed 33 patients that presented with symptomatic atherosclerotic lesions and luminal stenosis at about 50-70% and was confirmed in previous cerebrovascular angiography assessments (IBID). The cerebrovascular angiography provides a way to image blood flow with a dye to assess blood flow in the brain. Subjects additionally underwent the fractional pressure ratio procedure to assess distal and proximal pressure flow relative to stenotic lesions (IBID).

The results of this study showed that the TCD pulsatility index distal to the area of stenosis demonstrated a strong correlation with the fractional pressure ratio (IBID). This means that the pulsatility index used to quantify blood flow velocity at the nearest distal location may be indicative of the fractional pressure ratio, which implies that the non-invasive TCD tool used for assessment may provide enough information to make informed decisions relative to treatment for cerebrovascular stenosis disease (IBID). TCD has been used by many researchers and remains effective for the measurements of cerebral perfusion pressure and distal cerebrovascular resistance (IBID). Additionally, correlates exist relative to vascular resistance, intraluminal pressure, and fractional flow reserve (IBID). However, a lack of continued scientific evidence on the pulsatility index

hinders the adoption of this sole technique for adequate decisions made relative to cerebrovascular stenosis disease treatment (IBID).

This study was highlighted due to the linkage between TCD and cerebrovascular disease because in earlier discussions of this text, the correlation was made between AD and cerebrovascular disease. The conclusions drawn relative to this overlap provide evidence as to why TCD should be considered in the preliminary assessment of subjects with cardiovascular disease as these outcomes may be predictive of one's future cerebrovascular state and potential to develop a neurodegenerative disease such as AD. TCD as an inexpensive assessment modality may be able to provide clinicians with information that can be more closely monitored throughout the AD subjects disease trajectory or even before the disease develops. If cerebrovascular assessment can be incorporated as a preventative tool to screen patients that may be at risk for neurodegenerative disease, this in turn can help identify the disease earlier on and may even provide further support for a more confirmed diagnosis.

Ultimately, this can then lead to an earlier integration of more effective treatment methods as clinicians will be equipped with more sufficient information over time. This case analysis takes into consideration the lack of current information that exists between TCD and AD, however, the analysis aims to pose an alternative perspective for how neurodegenerative diseases such as AD can be monitored prior to symptom presentation and maybe even before the disease presents entirely. This shift in perspective subsequently allows for a more open viewpoint on how neurodegenerative diseases can be observed, which acknowledges the potential for earlier treatment intervention and preventative disease management.

Increased quality of life scores may also benefit from earlier diagnostic protocols either for preventative measures or disease management, as well as earlier treatment interventions. The HRQoL score which assesses physical, psychological, and social states relative to the disease impact may in fact increase as a result of earlier diagnostic and treatment protocols (Batista and Pereira, 2016). Diagnostic and treatment factors can impact how a patient may respond to their current state and with earlier intervention their current state may present with more positive scores relative to their daily life. The QoL-AD that incorporates information from both the patient and the caregiver's point of view may also have the potential to increase, especially if patients can receive treatment earlier on in the disease process and these treatments can be proven as highly effective (Barbe, et al. 2018).

The disease management process either in the preliminary stages or prior to a confirmed diagnosis as a preventative measure can help to relieve the burdens that patients and caregivers carry due to the integration and involvement of more adequate care. The care clinicians currently provide could be considered acceptable, as this may be the most they can provide given the circumstance, however, when clinicians can provide alterative options because the disease was caught or managed earlier on, this in turn can directly affect how a patient views their current disease state. Additionally, caregivers may feel a lift of this burden because more thorough involvement in the initial stages of the disease assessment based upon other underlying comorbidities could potentially help clinicians identify a pathology sooner and thus push towards an earlier treatment intervention and relieve the caregiver with a slower disease progression.

These assumptions are solely based upon current research studies and data relative to AD and neurodegenerative diseases. Support for these statements would require researchers to not only study these preliminary methods for diagnosis, but also consider the quality of life and humanistic aspect to care throughout the entire disease journey. The correlation needs to be made between more effective diagnostic and treatment modalities for neurodegenerative diseases like AD and the quality of life for both patients and caregivers. Studies seem to target one or the other and fail to integrate both quantitative and qualitative outcomes in these scientific studies. The qualitative data relative to a patient or caregivers neurodegenerative disease process can provide evidence that may help clinicians confirm a diagnosis earlier on or even help to prevent the development of a disease like AD because the clinician remains integral in the patient's health journey.

An example of earlier treatment intervention based on current diagnostic protocols can be seen in a study completed by Rezai, et al. This study aimed to assess the effects of aducanumab and FUS on patients with confirmed AD diagnoses (Rezai, et al. 2024). This study took 3 subjects that were diagnosed with mild cognitive impairment due to AD or mild AD dementia based on criteria from the National Institute of Aging-Alzheimer's Association (IBID). These individuals had received an AD diagnosis within a year prior to the start of the study (IBID). This remains critical relative to the argument for why earlier treatment intervention should be considered for increased quality of life from both the patient and caregivers' perspective. The fact that these subjects were diagnosed with a mild degree of the disease and considered for this proof-of-concept trial, demonstrates how researchers and clinicians have considered earlier intervention as

crucial in order to slow the progression of the disease and help alleviate poor quality of life outcomes.

The criteria of this study required subjects to elicit abnormal accumulation of Aβ levels that were greater than 1.4 for the standardized uptake value ratio in areas of the brain like the middle temporal gyrus, inferior temporal gyrus, temporal pole, superior frontal gyrus, middle frontal gyrus, precuneus, supramarginal gyrus, angular gyrus, and superior parietal lobule that are commonly associated with AD (Rezai, et al. 2024). Additionally, these participants needed to demonstrate elevated phosphorylated tau levels within the cerebrospinal fluid and evidence of cognitive loss (IBID). The criterion demonstrates how advanced the disease may appear relative to quality of life for patients and caregivers as the indications such as cognitive loss could evoke various mental and emotional issues post-diagnosis. The fact that this study aimed to provide earlier treatment intervention for mildly diagnosed patients remains critical for future research relative to FUS with the addition of therapeutics.

The treatment approach for this study used LIFU with MRgFUS techniques to open the BBB in confirmed AD patients for the administration of aducanumab, an anti-Aβ antibody, which has been shown to slow the progression of AD in stand-alone treatment (Rezai, et al. 2024). Each subject received FUS to open the BBB followed by aducanumab infusion treatment for 6 months (IBID). The treatments were monitored post-drug-delivery with gadolinium injections and MRI to confirm proper closure of the BBB at 24 hours and again at 48 hours post-treatment (IBID). Neurological assessments were performed 30, 60, 90, and 180 days for follow-up evaluation and also include 12- and 18-month follow-ups with projected follow-ups for the next 5 years (IBID).

Results of this study showed greater quantifiable reductions in Aβ levels confirmed with the standardized uptake ratio and centiloid values (Rezai, et al. 2024). The 3 subjects showed on average a 32% reduction in the standardized uptake ratio after 26 weeks relative to the regions of the brain that received the combined 6 consecutive treatments of drug therapy and FUS (IBID). The areas that were not treated with FUS, but did receive drug therapy were shown to have less reduction in Aβ levels compared to regions that received both FUS and drug delivery correspondingly (IBID). This data shows that Aβ reduction was more effective when combined with FUS and should continue to be considered in future research. Since the data outlines how FUS combined with the anti-Aβ antibody aducanumab was successful for the reduction of Aβ levels in the treated regions, future research may now aim to identify how the cost of this treatment compared to stand-alone drug treatment may be more advantageous for patients. Additionally, future research can determine how this therapy with targeted drug treatment delivery may not only be more cost-effective for patients, but also provide more successful treatment outcomes.

The limitations to this study are centered around the fact that only 3 subjects were assessed. The future of this research would need to include more subjects to continue to validate the data and conclusions that have been drawn. A positive component to this research relative to the science, has shown that this combined therapy produced effective results. A secondary issue that should be considered and addressed would be to determine how this can be cost-effective for patients, as economic burden has been highlighted as a quality-of-life factor that can affect both patients and caregivers. If future research can show that this combined therapy can alleviate economic stress along with physical,

mental, and emotional factors that can hinder one's quality of life as a result of diseases like AD, then this early proposed treatment method for patients could completely change the lives for those with the disease or those left with the burden to care for the disease.

Parkinson's Disease:

Currently, no predominant imaging modality exists in routine use cases for the diagnosis of PD and other related parkinsonism conditions that involve slow movements, stiffness, or tremor (Durmaz, et al. 2023). PD involves the loss of dopaminergic neurons in the pars compacta of the substantia nigra, which makes the substantia nigra a region of interest for researchers (IBID). The substantia nigra has been considered in various research studies due to the hyperechogenic response this region elicits in transcranial ultrasound imaging (Mei, et al. 2021). Additionally, the image display typically utilized to see this hyperechogenic response can be referred to as the B-mode display (Durmaz, et al. 2023). Transcranial B-mode sonography allows for the visualization of brain parenchyma through the temporal acoustic window and can be commonly used to measure echogenic responses of the substantia nigra in PD cases (IBID). Transcranial sonography can also be used to perform a thalamic examination, red nucleus examination, and even atrophy of various regions, all of which can be indicative of different movement disorders (IBID).

Transcranial ultrasound has been shown to be inexpensive, fast, and easy to implement, which makes this tool valuable as a patient centered diagnostic approach (Durmaz, et al. 2023). One study assessed the reliability of transcranial ultrasound in the diagnosis of PD and how this tool may be able to help differentiate PD from other movement disorders with similar symptom representations (IBID). There were 102

participants in this study that consisted of 48 healthy individuals, 45 PD patients, and 9 that showed symptoms of other movement disorders (IBID). The sonographers for this study were blind to whether the subject was a healthy individual, PD individual, or had another movement disorder (IBID). The purpose of this distinction was to force the sonographers to give an honest response relative to the echogenic response of the substantia nigra.

The results showed that the hyperechogenicity of the substantia nigra significantly increased in the PD group in comparison to the other movement disorder and healthy controls group Durmaz, et al. 2023). This shows that the substantia nigra of the PD group demonstrated such echogenic distinction that the sonographers blind to the disease state of the individual were able to identify a more prominent response. This allowed researchers to place emphasis on the fact that transcranial ultrasound could be a plausible tool for the diagnosis of PD.

Additionally, other research has shown that the hyperechogenicity of the substantia nigra did not change in size or width relative to the disease duration, which suggests that this data may be represented in the preclinical period of PD (IBID). The pre-clinical PD phase can be understood as the phase where a pathology has begun and biomarkers indicative of PD may be found (Dommershuijsen, et al. 2021). An important aspect to note about the pre-clinical PD phase remains centered around the fact that no symptoms of the disease have presented (IBID). This remains noteworthy relative to transcranial ultrasound as an early diagnostic technique for PD because this approach may be able to be utilized as an assessment tool prior to the onset of symptoms, which

can aid in earlier treatment intervention. This can be further supported from research that has shown the correlation between cerebrovascular disease and PD (Brisson, et al. 2023).

The hyperechogenic response in the substantia nigra has been hypothesized to be a result of iron accumulation, which has been believed to be a contributor to the dopaminergic neuron degeneration found as a result of the PD pathology (Durmaz, et al. 2023). The overload of iron in brain tissue has shown to be increased in patients with cerebrovascular disease (Brisson, et al. 2023). One study even showed how iron deposition in the globus pallidus of PD patients with both the AR and TD phenotype was present (IBID). Although the globus pallidus differs from the function of the substantia nigra, they both work within the same network of communication relative to dopaminergic neurons, which further emphasizes the correlation between cerebrovascular disease and PD.

This data remains important relative to a patient's quality of life and care because these assessment tools can be utilized to assess patients that may be in the pre-clinical stages of PD or at risk for the development of PD due to their indications of cerebrovascular disease or iron deposition. This does not mean that all patients who develop PD have excess iron accumulation in brain tissue or have underlying cerebrovascular disease, but this does mean that researchers have shown correlations between the two factors, and they should therefore be considered in pattern recognition analysis for the PD disease pathology. If patients that have underlying cerebrovascular disease or excess iron accumulation are at risk for the development of PD, then assessment tools like TCD and other forms of transcranial ultrasound should be considered as an earlier diagnostic technique. This remains especially true for the cases

where a hyperechogenic response of the substantia nigra exists, as this has been shown to not alter in size throughout the disease duration (Durmaz, et al. 2023).

Future research could aim to address how the hyperechogenic response of the substantia nigra correlates with TCD assessment in patients with PD. This would then allow for a stronger correlation between cerebrovascular disease and PD relative to the echogenic responses seen with transcranial ultrasound images. Additionally, this data could then be used to determine how PD could be assessed earlier on, or how clinicians can identify risk factors prior to the onset of the disease.

Earlier diagnostic protocols such as transcranial ultrasound and TCD may help to identify indications of the PD disease pathology earlier on in the disease process. This would help increase quality of life scores in both patients and caregivers because access to earlier treatment intervention may be more readily available. Treatment interventions that can slow the disease progression and essentially preserve any physical activity or movement that PD patients have may help to increase quality of life for both patients and caregivers. Physical activity and the interactions with motor and non-motor symptoms of PD have been shown to be associated with HRQoL (Duvdevani, et al. 2024). Increased physical activity has been shown to be associated with higher function and increased quality of life especially true for patients with PD (IBID). This then would also help to increase quality of life scores for caregivers as patients can have a stronger chance to maintain their own autonomy and function (Chekani, et al. 2016). Further research would need to support the current use of transcranial ultrasound and TCD as early diagnostic mechanisms for the PD pathology in order for clinicians to adopt these methods into practice. Unfortunately for TCD and transcranial ultrasound assessment, limitations do

exist that hinder a practitioner's ability to properly assess blood flow in certain regions of the brain due to anatomical interferences relative to bone window (Durmaz, et al. 2023).

A limitation that exists for these proposed solutions relates to the temporal bone window where the probe can be placed to image the cerebrovascular structures and determine the velocity of blood flow (Durmaz, et al. 2023). The temporal bone window has been shown to be insufficient for about 10-15% of the general population and can reach up to 25% with age and even women post menopause (IBID). This limitation may hinder the ability for this early diagnostic tool to be adopted, as a majority of the individuals diagnosed with PD are 65+ years of age (IBID). Further research needs to be completed relative to this scope to address this potential hurdle for the implementation of transcranial ultrasound and TCD as an early diagnostic technique for PD. Research supports that when these tools have a visible window to image, the echogenic results are clear in addition to vascular flow, which therefore shows that the information presented can be valuable for the potential early confirmation of PD. This signifies why this technique should be considered; however, clinicians will need to adapt or find a way to include the percentage of individuals that do not have a sufficient temporal bone window for image acquisition. There may be a way to use the TCD approach for adjacent vessels to determine if the blood flow of those vessels provides insight relative to the PD pathology, but again would need to be considered in future research to find if these possibilities hold any type of validity.

If these gaps in research can be overcome, then more promise may be held for earlier integration of treatment interventions and potential to increase quality of life scales for both patients and caregivers. The lack of research in this area at current may

place a slight temporary setback to early PD diagnostic techniques, however, the advancements in the area of PD treatment have continued to grow exponentially, which could possibly make up for these present-day limitations.

Current treatments for PD include therapeutic approaches and stereotactic surgery like DBS (Krishna, et al. 2023). DBS has been performed to target the globus pallidus internus through the use of high-frequency electrical stimulation through an implanted device (IBID). The role of the globus pallidus revolves around conscious and proprioceptive movement control (Javed & Cascella, 2020). The globus pallidus internus remains responsible for output information to the thalamus, which can be referred to as a relay station for motor and sensory signals (IBID). Studies have shown that the overactivity of the subthalamic nucleus due to a loss of dopamine can increase activity of the substantia nigra and globus pallidus internus, which directly correlates to cortical motor function and activity (Lu, et al. 2023). DBS treatments have been found to be successful in the reduction of involuntary motor symptoms as a result of PD (Krishna, et al. 2023). This procedure can even be performed in both cerebral hemispheres to control bilateral symptoms of PD and has been the main surgical approach for patients with PD who have inconsistent effectiveness of the therapeutic PD drug Levodopa (IBID). The limitations to DBS as previously outlined can be attributed to the fact that this procedure stands as an open surgical approach that carries a risk for intracranial bleeds and infection (IBID). Additionally, this procedure can be viewed as intrusive by patients and the implanted device requires management, which can be limited for patients that do not have access to those services (IBID).

The concept of FUS has surfaced overtime as a more favored option to treat PD symptoms due to the non-invasive approach with relatively similar, if not more effectiveness than the invasive DBS procedure. This treatment can also be referred to as an MRgFUS approach because of the FUS and magnetic resonance imaging combination used to monitor tissue temperature through simultaneous targeted ultrasound beam delivery (Krishna, et al. 2023). The localization step for this procedure involves low energy sonication to the relative target to ensure optimal target location and to determine whether the patient presents with any preliminary side effects (IBID). After the localization process has been completed, permanent ablation subsequently follows (IBID). This two-step process takes into consideration patient care and quality of life with meticulous calculations to safeguard the effectiveness of treatment. This process places patient care and quality of life at the forefront of this medical treatment in comparison to the DBS procedure because MRgFUS uses a real-time thermal ablation map to track heat sensitivity of adjacent areas.

The DBS procedure typically does use some sort of navigation equipment to place the targeted lead; however, this process typically involves a drill into the patient's skull with manual placement of the lead. There are not as many checks during the DBS procedure to determine if adjacent tissue damage has happened unless the surgeon tracks motor movement throughout the surgery. Patients are not typically fully sedated in this type of procedure because dependent upon the stage of the surgery, the surgeon wakes the patient up in the middle of the procedure to see if the lead placement and stimulation stops the tremors. Aside from the initial invasive portion of the procedure, this subsequent step may be why patients consider this treatment unacceptable (Krishna, et al.

2023). The only advantage of the DBS procedure as opposed to MRgFUS remains centered around the fact that lesion created by the lead and stimulation in DBS procedures can treat progressive symptoms due to the ability to modify the lesion post-procedure (IBID). In MRgFUS the total ablation of that target hinders one's ability to modify that targeted area post-ablation (IBID).

Additionally, some clinicians have even placed leads in FUS ablated regions due the symptom progression of those patients with PD (Krishna, et al. 2023). There will always be pros and cons to both treatment methods and some researchers and clinicians may advocate for one treatment over the other, however, when patient quality of life stands at the forefront of the decisions made, one may consider a less invasive approach like MRgFUS because similar immediate effects can happen as a result without the hindrance of invasive procedural side effects. Further assessment on what studies have been completed at current, relative to a patient's quality of life may shed more light on the most optimal treatment methods for patients with PD. The adoption of MRgFUS should still be considered relevant, as this approach may present as a more acceptable treatment modality for patients with PD relative to their quality-of-life post-diagnosis.

A study completed by Krishna and colleagues assessed how unilateral ablation of the internal globus pallidus with MRgFUS affected motor symptoms in PD patients with medication-refractory (Krishna, et al. 2023). The total population of this study consisted of 94 patients, 65 of which underwent the ultrasound ablation treatment, and 25 that were part of the control group who received the sham procedure (IBID). The results of this study showed that the unilateral focused ultrasound ablation approach to the internal globus pallidus significantly reduced Levodopa-induced dyskinesia and motor severity

scores opposite to the treated side at 3 months (IBID). Additionally, the MDS-UPDRS IV score which assesses motor complications of medical therapy, improved by 5.1 in the FUS ablation treatment group compared to 0.3 in the sham control group from baseline to month 3 (IBID). This means that the treatment group with FUS reduced their motor complications due to medication-refractory greater than the control group. This shows that the FUS treatment was effective for the reduction of motor complications due to Levodopa-induced dyskinesia.

This study showcases significant discoveries relative to the effects of FUS on the internal globus pallidus for Levodopa-induced dyskinesia, however, one may question why FUS ablative techniques were not tried for patients with more recent diagnoses or individuals that had not opted in for Levodopa therapeutic treatment. The reason for this could be because this type of treatment may not be FDA approved for more recent diagnoses without Levodopa or other PD therapeutic drug intervention, or because therapeutic drug intervention remains the standard first-line approach for initial treatment. Regardless for the reasons behind this, FUS treatments should be studied as a first-line therapy for recently diagnosed PD patients due to the effectiveness that has been shown in various studies. These FUS approaches could be utilized to either ablate certain targeted regions or even to open the BBB for effective Levodopa drug treatment delivery. The point remains that the adoption of FUS techniques should continue to sit at the forefront of medical research and advancements because this approach has the potential preserve patient quality of life in addition to the potential reduction of adverse risks associated with more invasive treatment options.

Amyotrophic Lateral Sclerosis:

ALS can be typically understood as an upper motor neuron and lower motor neuron degenerative disease, where current tests aim to identify upper and lower motor neuron functionality through the El Escorial and Awaji criteria (Hobson-Webb and Simmons, 2019). Upper motor neuron degeneration can be diagnosed clinically, while lower motor neuron degeneration can be typically examined through the use of nerve conduction studies as well as clinical examination (IBID). Electrodiagnostic studies aim to assess variations in waveforms associated with movement, in addition to spontaneous activity (IBID). The physical exams focus on spastic movement, muscle twitches, and muscle atrophy or weakness of limb movement (IBID). The current ways established for the diagnosis of ALS can be used for assessment when symptoms present. This shows that current diagnostic protocols for ALS prior to symptom presentation are most likely limited, which can affect patient quality of life given that the life expectancy of ALS patients has been shown to be 2–4-years after the initial diagnosis (Meng and Lipsman, 2021).

Ultrasound remains another form of diagnostic assessment for ALS, however, these protocols are still used once symptoms present. The limited research around ALS makes this disease difficult to diagnosis prior to the onset of symptoms. This means that a systematic review of current patient studies remains critical for the comprehension of how future researchers may be able to find more efficient ways to diagnosis ALS earlier on in the disease process. Ultrasound can be seen as a beneficial tool to explore given that research between ultrasound and ALS dates back to many decades (Hobson-Webb and Simmons, 2019). Ultrasound for ALS diagnosis has been shown to be more effective than

electrodiagnostic studies in the assessment of muscle atrophy and sporadic movement due to an increased field of view in contrast to the recorded area of an electromyography needle (IBID). One study even showed out of 81 patients studied, only 48% were diagnosed with definite ALS with the use of the El Escorial criteria compared to the 79% confirmed ALS diagnoses with the ultrasound-assisted Awaji criteria (IBID). This study demonstrates how ultrasound has helped clinicians gain more insightful information compared to electromyography, that may further lead them to a more definitive ALS diagnosis, while also viewed as less invasive due to the fact that electromyography can sometimes be performed with the placement of a needle directly into the muscle (IBID). The less invasive and readily available approach of ultrasound makes this tool more optimal for patients as this can help to reduce added stress and anxiety that may present when patients are required to undergo these types of assessments.

Additionally, the fact that ultrasound has been viewed as superior compared to electromyography for the assessment of muscle functionality shows that the reliability of ultrasound from a clinical point of view remains highly supported. This data allows one to question how ultrasound could be utilized as a preliminary assessment tool to obtain a baseline of muscle atrophy as an individual ages to determine whether or not they may fall within a range that could be considered early stages of the ALS disease. The problem remains that clinicians may not have a reason to explore this pathology due to the limited presentation of symptoms, however, with the knowledge that researchers and clinicians have obtained over the years relative to ALS, preliminary protocols may be worth further consideration.

Currently established ultrasound diagnostic measures are relevant for the assessment of physical degeneration commonly associated with ALS; however, research also supports how cognitive dysfunction presents as a result of motor neuron diseases like ALS (Murphy, 2008). The limited research on cognitive dysfunction and ALS could possibly be attributed to the fact that in the past, little to no attention was paid to cognitive symptoms, as the rapid neurodegeneration and mortality outweighed any recognition of cognitive decline (IBID). Cognitive dysfunction relative to motor neuron diseases can be found in research that dates back to 1932, which shows how cognitive decline presented in ALS cases in some way shape or form (IBID). Research currently acknowledges that upwards of 50% of ALS patients demonstrate some sort of cognitive impairment and about 20-30% of them fulfill the criteria for frontotemporal dementia (IBID).

The linkage between cognitive impairment and ALS remains important to understand because one study that looked at cognitive function and associations relative to primary lateral sclerosis, an upper motor neuron only disease, showed that cognitive dysfunction was associated with cerebral hemodynamic disturbances directly related to the level of cognitive impairment (Murphy, 2008). Primary lateral sclerosis remains similar to ALS as they both can be classified as a motor neuron disease, despite the singular presentation of upper motor neuron degeneration in primary lateral sclerosis (IBID). Research shows the correlation between cognitive dysfunction and cerebral hemodynamic disturbances in primary lateral sclerosis, which creates room for one to infer how similar trends may be present in ALS cases (IBID).

The connection between cognitive impairment and cerebral hemodynamics ties TCD back in as a potential diagnostic tool for ALS and possibly an earlier assessment tool than ultrasound for the evaluation of physical degeneration typically performed at the onset of ALS symptoms. Limited data exists that correlates how the use of TCD could be used in early ALS diagnostic assessment, which means that many inferences must be drawn between data that researchers and clinicians have uncovered over the decades of research. The fact that ultrasound has been supported in ALS research for decades illustrates how this readily available and non-invasive solution still remains at the forefront as a patient centric diagnostic solution.

The importance of these conclusions remains relevant for the support of TCD as a potential tool for the early diagnosis of ALS because research has supported that cognitive dysfunction has been shown to be present earlier on in the ALS disease progression and how cognitive dysfunction can be correlated with cerebral hemodynamic disturbances that can be currently analyzed with TCD to assess blood flow (Murphy, 2008). The link between cognitive dysfunction earlier on in the ALS disease process and the supported association of cognitive dysfunction to cerebral hemodynamic disturbances, illustrates a potential pathway of exploration for the integration of more preliminary diagnostic interventions for diseases that have limited research like ALS. The reason for this remains centered around the fact that assessment tools like TCD are already used to measure blood flow in other disease pathologies and disorders. If theoretical correlations can be linked to present a stronger argument for why TCD should be used in preliminary diagnostics for patients that may be at risk to develop ALS, then clinicians can begin to implement these standards earlier on throughout a patient's life,

which can aid in the improvement of overall quality of life and quality of care for at risk patients.

Cerebral hemodynamic disturbances such as reduced blood flow can commonly be seen in individuals with cerebrovascular disease and have been supported in ALS studies that highlight small vessel size as a result of the ALS pathology (Schreiber, et al. 2023). Additionally, ALS patients have been shown to present with lowered endothelial growth factor levels essential for the formation of blood vessels (Brisson, et al. 2023 & Schreiber, et al. 2023). Endothelial dysfunction has also been identified as one of the early signs in the atherosclerotic process associated with cardiovascular disease (Shah, et al. 2008). Atherosclerosis may develop in multiple sites simultaneously as the circulation pathways of the heart, brain, and peripheral systems can be affected by similar risk factors (IBID). These discoveries correlate how vascular dysfunction in different regions of the body can present similarly due to comparable risk factor associations. This means that cardiovascular diseases like atherosclerosis could possibly start in vascular regions of the heart and subsequently also present in regions of the brain as cerebrovascular disease due to the exposure of the same risk factors. This remains relevant to ALS because one possible starting point for the disease process could potentially begin with patients that either present or are at risk for cardiovascular disease.

A systematic review by Kioumourtzoglou, et al. aimed to assess risk factors of cardiovascular disease with the ALS pathology (Kioumourtzoglou, et al. 2016). This study utilized Danish hospitalization data to assess the patient's cardiovascular disease history prior to the day of the patient's confirmed ALS diagnosis (IBID). This means that the researchers took the patient's ALS diagnosis as a preliminary marker to perform a

regression analysis on prior cardiovascular history. Researchers then took that data from the confirmed ALS diagnosis group and calculated an odds ratio based on the acquired cardiovascular data (IBID). This calculated odds ratio was then used as a metric tool for the control group of patients that did not have a confirmed ALS diagnosis, but did present with cardiovascular disease history, to determine the likelihood of a potential ALS diagnosis in the future (IBID). The odds ratio was calculated at 3, 5, and 10 years (IBID). This study found that cardiovascular disease diagnosis prior to the index date or the date of a confirmed ALS diagnosis in the ALS group was associated with a higher rate of ALS prediction in the control group (IBID).

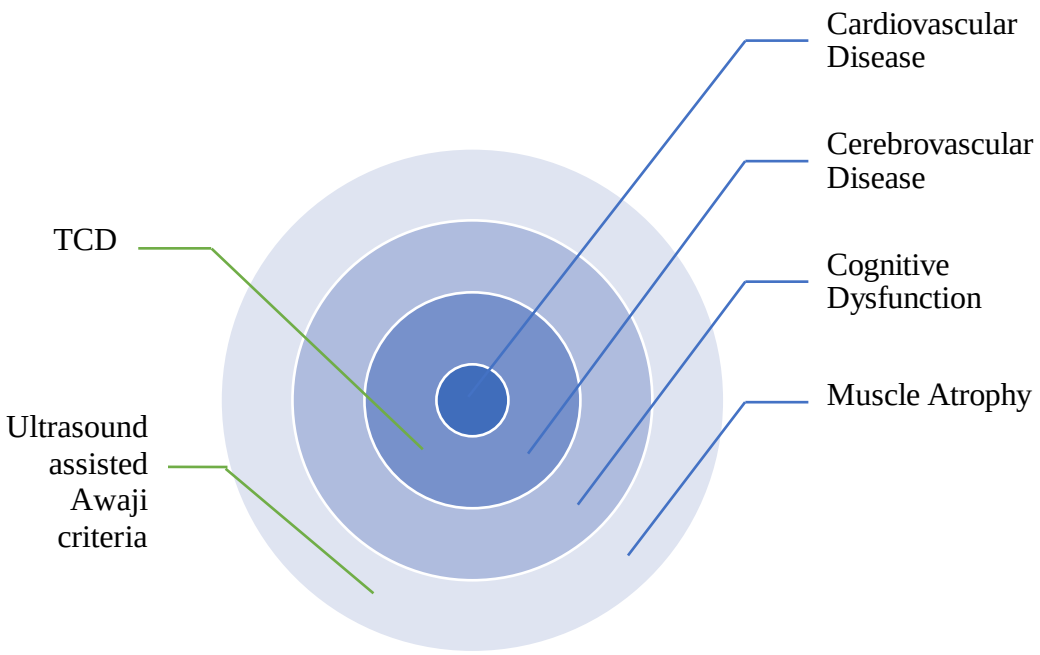
This predictive trend provides potential reason to believe that early cardiovascular disease may suggest insight into the later confirmed diagnoses of ALS patients. The additional data from Shah, et al. also supports this argument. The study by Kioumourtzoglou, et al. does have a few limitations given the predictions may only hold validity if subjects were followed throughout their lifetime to confirm whether or not the odds ratio and likelihood of an ALS pathology was in fact accurate and reflective of the original hypotheses and calculations, however, the conclusions drawn still provide enough probable evidence that the ALS pathology may begin with cardiovascular and cerebrovascular issues and should be considered for more thorough analysis.

The supportive ALS studies that correlate cardiovascular disease, cerebrovascular disease, cognitive dysfunction, and motor neuron degeneration warrant the need for a theoretical visualization of how these processes could be represented, as this can help one to further understand why TCD should be considered as a preliminary assessment tool for ALS. Figure 2 shown below demonstrates a relational theoretical framework based upon

the clinical information that remains known relative to physical and cognitive symptom presentation and other diseases that can potentially contribute to the identification of ALS through other underlying comorbidity factors. Additionally, TCD as an assessment tool and the ultrasound assisted Awaji criteria utilized for the evaluation of muscle atrophy and spasms are labeled on the left side of the figure in parallel to the clinical indications labeled on the right side of the figure.

Figure 2

Theoretical Disease Framework of ALS and Associated Assessment Tools



Note. A proposed representation of the ALS disease progression and state relative to the presentation of symptoms and associated assessment tools.

Figure 2 aims to represent a theoretical visual representation of the ALS disease progression which can be seen with clinical signs and symptoms on the right with the correlated assessment tool on the left. Muscle atrophy and cognitive dysfunction are

highlighted on the outermost circles to show how these clinical signs and symptoms appear in ALS research as the most common indicators of the disease representation. Additionally, muscle atrophy has been shown to be one of the most visible indications of the disease as well as cognitive dysfunction, however, cognitive dysfunction remains less visible in initial assessments compared to muscle atrophy. Therefore, cognitive dysfunction remains further inward on the relationship scale. The relationship scale simplifies even more into cerebrovascular disease and at the core, cardiovascular disease, to theoretically illustrate how far back in the disease process ALS may begin relative to the progression of visual symptoms later throughout the disease journey. Ultrasound assisted Awaji criteria sits in the same ring as muscle atrophy because this assessment tool can be used to evaluate muscle degeneration in patients with ALS. The TCD assessment tool sits in the same ring as cerebrovascular disease due to the research that supports this tool for the assessment of blood flow functionality in patients with cerebrovascular disease.

The theoretical framework proposes that the ALS disease process may in fact begin at the cardiovascular disease stage and branch out into cerebrovascular disease, which then can move into visible symptoms like cognitive dysfunction and muscle atrophy. If this visual theory was in fact reflective to the ALS pathology prior to when patients present with physical signs and symptoms, this diagram would necessitate the demand for more integration of preliminary screening protocols for patients with cardiovascular disease or underlying cardiovascular and cerebrovascular comorbidities. This would then allow for clinicians to implement preventative evaluation practices that aim to screen for cardiovascular or cerebrovascular dysfunction with the goal to provide

earlier treatment intervention or monitorization of patients more closely overtime. A standardized preventative practice such as this would elevate the patient centric approach for ALS disease management and potentially increase patients' and caregivers' quality of life. Clinicians would also be more closely tied to the patient's journey which can help to deliver the most optimal treatment outcomes overtime.

The studies previously analyzed in Part Two from Abrahao, et al. and Shen, et al. happen to be some of the most current case studies performed relative to ALS and FUS treatment (Abrahao, et al. 2019 & Shen, et al. 2023). The study by Abrahao, et al. was the first-in-human trial performed to see if FUS could open the BBB, while Shen, et al. generated assessment with mouse models. The results from both studies highlight the effectiveness of FUS in ALS treatment and also have opened the door for further research in this field. Due to the limited current research on FUS and ALS there are not many other case studies to highlight for this section and all references of the outlined cases should be reviewed in Part Two. The importance to touch upon in this section relative to the Abrahao, et al. and Shen, et al. studies remain centered around the benefit these treatment options have on ALS patient quality of life.

Research has shown that respiration becomes one of the most affected areas post-diagnosis for ALS patients because weakness occurs as a result of muscle degeneration and atrophy (Kvam, et al. 2023). The amount of time patients typically have with minimal assistance in respiration sits around 34.7 months, but can vary based upon the severity of the case (IBID). This means that patients and their caregivers are not only required to deploy a care management plan post-diagnosis, but also account for the potential severity of progression. Pharmacological treatments for ALS remain limited,

which means that non-invasive ventilation practices, nutritional guidance, and a multidisciplinary approach to care are the current scopes to be considered (IBID). The integration of FUS to open the BBB in ALS patients for more effective drug delivery can be revolutionary if shown to preserve patient life and slow the progression of the disease. The implementation of FUS to open the BBB for earlier drug intervention may also have the ability to offset the symptoms that present as a result of ALS like weight loss, inability to swallow effectively, speech dysfunction, and respiratory issues, which would help to increase patient and caregiver quality of life (IBID).

The integration of a FUS approach may also even help to reduce the economic burden of these multidisciplinary approaches overtime through the integration of a solution that can possibly be more effective. There are foundations like the Focused Ultrasound Foundation that aims to advance research in the areas like ALS with this more effective type of treatment and remains a step in the right direction to provide funding opportunities for researchers to increase the amount of available data. The initiatives that foundations and research institutions set to advance ALS treatment options will remain crucial to the quality-of-life barriers these patients and caregivers currently face. Hopefully in the years ahead, researchers can obtain more data to support FUS as an optimal treatment modality for ALS patients and simultaneously work to make this treatment available to patients at an affordable cost.

PART FOUR

Associated Costs for Ultrasound as a Diagnostic and Treatment Modality for Neurodegenerative Disease: Cost-Analysis

Background

Neurodegenerative diseases like AD, PD, and ALS pose a significant impact to the health and well-being of many individuals and serve an even greater public health threat and increased economic burden at current (Zahra, et al. 2020). Significant research has allowed for more thorough investigation on the pathology behind these diseases, however, not enough has been uncovered to confirm a definitive treatment approach (IBID). Additionally, diagnostic protocols for these diseases allow for confirmation typically after physical or cognitive degeneration of symptoms present, which can often be considered too late to treat based upon how quickly the disease progresses. These types of neurodegenerative diseases tend to increase with age and can exist for about 2-10 years, which ultimately results in the need for special care and treatment (IBID). The lack of early diagnostic methods that may help to assess risk for these neurodegenerative diseases later in life and unidentified confirmed treatment interventions in addition to the heavy economic burden associated with these diseases, affect patient and caregivers' overall quality of life.

Previous research in these sections highlight the potential benefit for the incorporation of preliminary assessment tools like TCD and other forms of transcranial ultrasound to identify risk factors that may be associated with the disease progression before the onset of symptoms occur. These preliminary assessment tools can provide clinicians with information relative to cardiovascular and cerebrovascular disease that

may be indicative of later neurodegenerative development. The associations made between AD, PD, and ALS relative to these conditions have been supported through the research of many different scholars (Graff, et al. 2023; Roher, et al. 2011; Brisson, et al. 2023; Schreiber, et al. 2023; Kioumourtzoglou, et al. 2016). The argument that neurodegenerative diseases may begin with risk factors associated with cardiovascular and cerebrovascular diseases pushes potential preliminary assessment tools to be more focused on cerebral hemodynamics and what the evaluation of blood flow may tell a clinician about the patient's current health state. The implementation of TCD as a preliminary assessment tool for individuals over the age of 60 to assess blood flow functionality should be considered given the associated risk factors that develop as a result of age supported by the average mean age of 60.1 in relevant studies (Allen, et al. 2023). The integration of a diagnostic tool such as TCD can help clinicians conceptualize how these risk factors and a patient's age at their current state can contribute to the potential development or progression into neurodegenerative diseases over time.

One barrier to this potential implementation may be centered around the fact that the use of TCD as either a preliminary or prevention assessment tool for neurodegenerative diseases remains uncommon. Current research supports how this tool may be valuable to provide further insight relative to cerebral hemodynamics of patients with associated neurodegenerative diseases and some studies even provide timeline regressions to predict how underlying cardiovascular issues may have been a contributor to the development of some later confirmed neurodegenerative disease cases (Roher, et al. 2011; Brisson, et al. 2023; Schreiber, et al. 2023; Kiommourtzoglou, et al. 2016). The lack of research that combines subsequent collective data to justify a potential argument

for why tools like TCD should be used may be the reason why the integration of these tools has been minimal for neurodegenerative disease diagnosis and overall patient disease journey evaluation. The purpose of this dissertation pulls together the collaborative data around these topics to defend the argument for why the integration of TCD should be considered.

Another piece of evidence to consider in conjunction to the data collected and outlined for the use of TCD as a potential preliminary assessment tool for patients either with or at risk for neurodegenerative diseases remains centered around the economic burden that these diseases produce. Studies have shown that estimated healthcare costs associated with AD treatment for 2022 were around $321 billion (Skaria, A.P., 2022). The PD total economic burden was estimated around $51.9 billion in 2017 and $1.02 billion for ALS based on data prior to 2021 (Yang, et al. 2020 & Berry, et al. 2023). This data collectively outlines how much impact and economic burden these neurodegenerative diseases have not only on patients, but also their caregivers. Additionally, this data provides insight into what the costs of these current approaches are and can provide further support for why the integration of preliminary assessment tools like TCD should be considered in neurodegenerative disease diagnostic protocols.

Moreover, the treatment associated with these neurodegenerative diseases can also be costly and not suitable for older patients who rely on government funds to cover healthcare costs because the average age of diagnosis ranges between 60-65+ years of age (Maresova, et al. 2020). The therapeutic approaches for some of these diseases can be greater than $10,000 and alternative procedural options may be considered invasive and not favored by patients (GoodRX, 2011-2024 & Krishna, et al. 2023). The non-invasive

MRgFUS techniques that currently exist as a treatment option for PD are only cited for use relative to PD and other movement disorders, which excludes other diseases like AD and ALS for consideration for these types of procedures, even though current research supports how FUS has been shown to be affective for neuromodulation and BBBO for earlier drug delivery (Hu, et al. 2023; Hosseini, et al. 2022; Baek, et al. 2022; Lu, et al. 2023; Cheng, et al. 2022; Shen, et al. 2023). Potential remains for the use of one payout code that highlights the use of FUS for ablation and therapeutic intervention, but has not necessarily been cited for use cases with AD and ALS specifically.

The purpose of this cost-analysis remains relevant to show how TCD costs compare to inpatient diagnostic stay costs, to advocate for the implementation of TCD as patient centric assessment tool. This dissertation incorporates a viewpoint to address how TCD implementation has the potential to help with earlier diagnosis of neurodegenerative diseases and the addition of this cost-analysis section aims to demonstrate how TCD remains a cost-effective method against a 1-night inpatient hospital stay. A similar comparison will also be assessed relative to current approved treatment options for invasive, non-invasive, and therapeutic approaches to further advocate for optimal treatment interventions for all patients with or at risk for neurodegenerative diseases. The goal of the treatment intervention cost-analysis section aims to provide cost associated data points for the justification of FUS as a treatment option for patients with neurodegenerative diseases like AD, PD, and ALS.

Methods

Data was acquired from United States Zip Codes database based off the U.S Census Bureau to determine the top 6 zip codes associated with a few of the largest cities

in the United States. Those locations were then input into the FAIR Health Consumer database with information from the American Medical Association to determine the associated hospital facility costs for inpatient diagnostic stays relative to neurodegenerative disease assessment and the outpatient out-of-pocket screening costs for a complete TCD ultrasound scan of the brain for patients. This data was acquired for a diagnostic comparison. Average means were calculated for total out-of-pocket TCD costs and inpatient diagnostic stay amongst 6 different zip codes. The percent increase was then calculated between TCD out-of-pocket costs and inpatient diagnostic stay. Percent increase between different zip codes was also calculated as reference for cost relative to geographic regions.

Relative to the treatment comparison, data was acquired from the CMS Release Cy 2022 Hopps Propose Rule produced by the American College of Radiology to determine the proposed payout based on the CPT codes 0398T and C9734 for MRgFus treatment intervention. Further data was investigated again from the FAIR Health Consumer database to determine the in-network hospital facility costs for a standard invasive procedural approach for the CPT code 00024 based on the zip code 11101 for New York. The New York zip code was used to provide an example of what one standard invasive procedure may cost for relative comparison to the noninvasive method. An estimated 70% coverage cost was calculated for these CPT codes based off the 70% coverage from data in the hospital facility costs for inpatient diagnostic stay compared to patient TCD out-of-pocket screen costs for comparable reference.

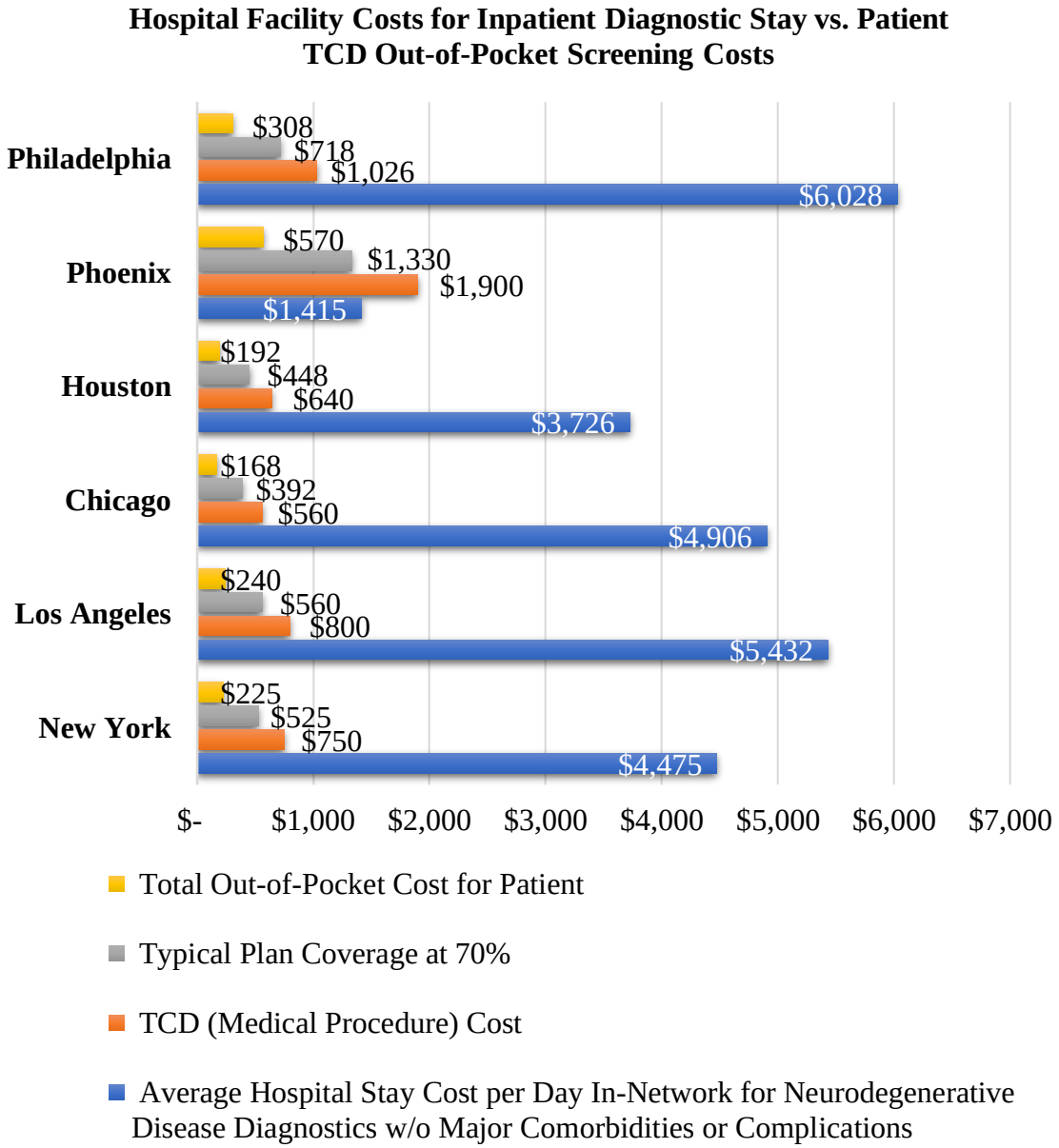
Costs associated for drug therapeutics were then obtained from the GoodRx database for current market drugs used to treat AD, PD, and ALS. Costs were acquired for the AD monoclonal antibody Leqembi, the drug Ongentys to control PD symptoms and increase dopamine to the brain, and the therapeutic ALS nerve protectant drug Exservan. These subsequent therapeutics were selected based upon the drug intention relevancy to current research.

Results

The average TCD out-of-pocket cost was calculated between 6 different zip codes highlighted in Figure 3. The mean TCD out-of-pocket cost was $284. The average inpatient diagnostic stays for a 1-day rate in-network was also calculated between the 6 different zip codes with a mean rate of $4,330 per 1-day stay. There was a 93% increase in cost between the inpatient diagnostic stay 1-day rate and the standalone TCD out-of-pocket cost for 1 TCD screening. Philadelphia had a higher inpatient diagnostic stay rate at $6,028 as compared to other zip codes. Philadelphia showed a 38% increase in inpatient diagnostic stay cost relative to Houston with the lowest inpatient diagnostic rate at $3,726. Phoenix had the highest TCD out-of-pocket cost at $570, which was 71% greater than Chicago with the lowest TCD out-of-pocket cost at $168 after a 70% typical plan coverage was added.

Figure 3

Systematic Review of Hospital Facility Costs for Neurodegenerative Disease Diagnostics Compared to TCD Complete Ultrasound within the Brain Patient Costs



Note. A comparison between the average hospital stays costs for neurodegenerative disease diagnostics without major comorbidities or complications compared to the patient out-of-pocket costs for a TCD complete ultrasound within the brain. Data generated using information from *FAIR Health Consumer Healthcare Expense Estimates*, by the American Medical Association. 2020, *Zip Codes by City*, by United States Zip Codes. 2024.

Table 1 shows the CPT data with the correlated proposed payout at $11,534.07 for CPT code 0398T for MRgFUS at a high intensity for movement disorders, while CPTC9734 had a higher payout rate at $12,630.52 for MRgFUS ablation and therapeutic intervention. The average hospital stay in network cost for CPT code 00024 correlated with craniotomy and major device implant with complex CNS principal diagnosis without major comorbidities or complications was higher than both CPT0398T and CPTC9734 at $36,732 for the zip code 11101 reflective of the New York region. An estimated 70% coverage was calculated for both the CPT0398T and CPTC9734 codes to reflect what insurance may cover based upon the 70% typical plan coverage for TCD outpatient evaluations. The estimated 70% plan coverage decreased the initial potential cost to patients for CPT0398T and CPTC9734 to $3,460.22 and $3,789.16 respectively. The proposed payout information for CPT0024 was not applicable and therefore did not have an estimated 70% coverage calculation.

Table 1

CPT Codes Associated with Proposed Payout, Estimated Coverage, and Total Costs to Patients Relative to Average Hospital Cost per Day In-Network for Neurodegenerative Disease Procedures

CPT Codes	Description of CPT Code	Proposed Payout	Estimated 70% coverage	Total Cost to Patient	Average Hospital Cost per Day In-Network
CPT-0398T	"Magnetic resonance image guided high intensity focused ultrasound (mrgfus), stereotactic ablation lesion, intracranial for movement disorder including stereotactic navigation and frame placement when performed" (American College of Radiology, 2021).	$11,534.07	$8,073.85	$3,460.22	N/A
CPT-C9734	"Focused ultrasound ablation/therapeutic intervention, other than uterine leiomyomata, with magnetic resonance (mr) guidance" (American College of Radiology, 2021).	$12,630.52	$8,841.36	$3,789.16	N/A
CPT-00024	"Craniotomy with major device implant or acute complex CNS principal diagnosis without major comorbidities or complications" (FAIR Health Consumer and American Medical Association, 2020)	N/A	N/A	N/A	$36,732

Note. Data was collected from the *CMS Release Cy 2022*, by the American College of Radiology. 2021. An estimated 70% cost was calculated based off coverage reports from the *FAIR Health Consumer Healthcare Expense Estimates*, by the American Medical Association. 2020. The average cost per day for the CPT-00024 is based off the New York zip code 11101 from the *FAIR Health Consumer Healthcare Expense Estimates*, by the American Medical Association. 2020.

Table 2 shows one example of a therapeutic agent used for the treatment of either AD, PD, or ALS with the respective associated drug cost. The neuroprotectant ALS drug Exservan had the highest drug cost around $9,059.00 at the lowest listing price compared to the AD monoclonal antibody Leqembi and the PD therapeutic Ongentys used to treat signs and symptoms of PD, where prices can be seen as low as $2,453.00 for the AD drug and $651 for the PD drug. The Leqembi cost was relative to 4 vials administered in a medical setting, the Ongentys cost was associated with a 30-capsule supply, and Exservan at 3 cartons with 60 pouches in each.

Table 2

Associated Cost for Therapeutics Agents Relative to the Neurodegenerative Disease AD, PD, and ALS

Therapeutic Agent	Description of Therapeutic Agent	Drug Cost
Leqembi	A monoclonal antibody used to treat Alzheimer disease. Aims to decrease amyloid buildup and slow down the progression of symptoms. (GoodRX, 2011-2024)	as low as $2,453.00 (4 vials)
Ongentys	Treats the signs and symptoms of Parkinson's disease in people that are also prescribed Levodopa. Aims to increase the amount of dopamine in the brain (GoodRX, 2011-2024)	as low as $651 (30-day supply)
Exservan	A form of Riluzole used to treat ALS. Works as a neuroprotectant to delay worsening of symptoms (GoodRx, 2011-2024)	as low as $9,059.00 (60 pouches)

Note. Data was collected from *GoodRx,* 2011-2024.

Discussion

The out-pocket-costs for a TCD outpatient evaluation were acquired from the FAIR Health Consumer Healthcare Expense Estimates seen in Figure 3 to assess the

difference in cost between a TCD assessment and the inpatient diagnostic costs associated with a 1-day hospital stay for patients covered by in-network insurance (FAIR Health Consumer, 2020). These costs were acquired under the diagnostic section of the FAIR Health Consumer database site listed as complete ultrasound of the brain with blood flow (IBID). The TCD assessment data was labeled as outpatient coverage and the hospital stay was issued under in-network inpatient coverage. The difference in network coverage based on the type of facility was purposely chosen to demonstrate the difference in cost between a TCD evaluation and a full hospital diagnostic workup for a 1-day hospital stay relative to a potential neurodegenerative disease diagnosis with evidence provided by each type of assessment.

Costs were gauged for 6 different zip codes to show variability in insurance coverage per state. The TCD out-of-pocket costs for an outpatient assessment were listed with a 70% estimated coverage from insurance companies by the FAIR Health Consumer database site, aimed to provide patients with estimated coverage values for diagnostics and other procedural applications (FAIR Health Consumer, 2020). This shows that in most cases 70% coverage can be estimated for this type of outpatient assessment.

The TCD out-of-pocket costs were 93% less on average compared to the mean inpatient in-network 1-day hospital stay for a diagnostic workup protocol for a potential neurodegenerative disease diagnosis with evidence provided by the assessments. This 1-day hospital stay does not include other direct costs that may be associated with the hospital stay, which means that the 1-day hospital stay could be significantly more than the estimated average of $4,330 per day. The average out-of-pocket cost for a TCD assessment was shown to be around $284, which demonstrates how a TCD assessment

can be more affordable than a 1-day stay in a hospital for an assessment relative to a potential neurodegenerative disease diagnosis.

Data shows that in AD, a reduction in the luminal area of the intracranial arteries remains present as a result of atherosclerotic vascular disease (Roher, et al. 2011). TCD has been shown to be more accurate in the prediction of AD compared to indirect correlation tests because TCD can provide information relative to the cerebral blood flow and pulsatility index used to assess the difference in systolic and diastolic blood flow in the brain (IBID).

Additionally, in some studies TCD was able to identify multiple cardiovascular issues indirectly discovered through examinations that would have remained undetected had clinicians not used TCD (Roher, et al. 2011). Similar data for PD and ALS also supports how cardiovascular and cerebrovascular implications are present in patients with these diseases, which shows how TCD can provide insight relative to these disease states and evidence to support whether certain individuals could be at risk for future development of neurodegenerative diseases based upon their cardiovascular and cerebrovascular assessments (Roher, et al. 2011; Brisson, et al. 2023; Schreiber, et al. 2023; Kiommourtzoglou, et al. 2016).

This means that TCD not only holds significant potential to provide clinicians with information needed to determine whether a patient may be at risk for a neurodegenerative disease, or to confirm the potential diagnosis of the disease with complimentary insights relative to cerebral vascular flow, but also shows how this assessment remains cost-effective for patients as evidenced by the data in Figure 3. This does not necessarily mean that clinicians will forgo all other neurodegenerative disease

diagnostic protocols, but this does mean that clinicians should consider the use of TCD as a preliminary assessment tool for patients that exhibit underlying signs, symptoms, and comorbidities of cardiovascular and or cerebrovascular disease to provide closer monitorization of the patient's health state given these factors are associated with the onset and progression of AD, PD, and ALS.

Age also remains relevant in this defense because many studies highlight how most cases of AD, PD, and ALS present as individuals 65 years or older (Yang, et al. 2020; Forbes, et al. 2004; Katsuno, et al. 2018). This means that the economic burden associated with AD at $321 billion and the PD total economic burden at $51.9 billion, followed by the ALS economic burden at $1.02 billion are more than likely associated with individuals <65 years of age (Skaria, A.P., 2022; Yang, et al. 2021; Berry, et al. 2023). The relevance of this data for economic burden directly correlates with the data in Figure 3 as evidence for why TCD should be considered in preliminary assessments to reduce this overall economic burden for each neurodegenerative disease. Additionally, given that most of these individuals are 65 years of age or older, many of them most likely rely on government funds through Medicare, which further supports why government funded insurance should also consider the benefit of TCD implementation to help assess individuals that may be at risk for AD, PD, or ALS because this can not only reduce the overall economic burden, but also help to diagnosis or prevent the development of these neurodegenerative diseases earlier on.

Figure 3 also shows how the cost of TCD, and inpatient hospital stay diagnostic evaluations varied per state. Philadelphia had the highest inpatient in-network hospital stay rate at $6,028 per day compared to Houston with the lowest rate at $3,726 per day.

TCD out-of-pocket costs were greater for the Phoenix region at $570 per assessment compared to Chicago with the lowest cost of $168. This data shows that private insurance coverage varies upon geographical location, which can hinder some individuals' ability to pay for healthcare costs or preliminary assessments associated with a neurodegenerative disease. Although these costs vary per region, the trend still shows TCD as more cost-effective when compared to inpatient in-network hospital stays. The variations in cost per region may not be as much of an issue for patients 65 and older because they more than likely rely on healthcare associated government funds like Medicare. The potential barrier may be more centered around the adoption of these preliminary assessment tools into the reimbursement platform for government funds like Medicare. Government funded healthcare programs should consider the research and discoveries that have been linked between vascular functionality and neurodegenerative diseases to advance change in the protocols that currently exist for neurodegenerative diagnostics and treatment interventions, so that patients and caregivers affected by these burdensome illnesses can not only have a fair chance to mitigate or control symptoms with earlier intervention, but also find economic relief throughout the disease management process.

The integration of these preliminary assessments as a way of prevention or monitorization of a patient's health at the age of 65 or older can aid in a clinician's ability to diagnose these diseases earlier on, which directly leads to the implementation of earlier treatment interventions that can result in more optimal patient outcomes. Additionally, these preliminary measures should also be considered by clinicians for patient's even younger than 65 years of age, as cardiovascular disease has been shown to have an incidence of about 40% for men and women ages 40-59 (Rodgers, et al. 2019). This

means that clinicians can integrate screening methods earlier on for patients that either have or are at risk for cardiovascular and or cerebrovascular disease, as a way to monitor the patient's health more closely, which allows for earlier treatment intervention when and if the patient's health state starts to present with signs and symptoms that may be indicative of diseases like AD, PD, or ALS. The adoption of these preliminary measures may help to reduce late-stage diagnosis at the onset of physical and cognitive decline, which could potentially make the treatment interventions that currently exist more effective overtime.

The data outlined in Table 1 show the proposed payout for the associated CPT codes relative to the described treatment approach. The CPT code 0398T as outlined by the American College of Radiology correlates to the high intensity MRgFUS procedure with lesion ablation for intracranial movement disorders (American College of Radiology, 2021). The CPT code C9734 more specifically states focused ultrasound ablation or therapeutic intervention with magnetic resonance guidance for cases other than uterine leiomyomata (IBID). Lastly, the CPT code 00024 correlates with the craniotomy procedure with the addition of a major device implant or acute complex CNS diagnosis without major comorbidities or complications (FAIR Health Consumer, 2020). CPT codes 0398T and C9734 are FUS procedures that use magnetic resonance guidance to navigate and monitor the beam region and intensity for target definition and preparation of the entry point into the skull to reduce potential adjacent tissue damage.

The difference between these two CPT codes based upon the descriptions shows that CPT code C9734 can be billed for therapeutic interventions or lesion ablation purposes for any procedure other than uterine leiomyomata. Further investigation on the

language that surrounds CPT codes 0398T and C9374 would need to be considered, as the American College of Radiology may have other stipulations or diagnostic requirements that permit the use of this intervention for reimbursement purposes. The CPT code 00024 can be reflective of invasive procedures like DBS used to treat movement disorders with tremors like PD, however, further research will need to be completed to determine if this exact procedure covers treatment for all PD diagnoses or just certain variations.

Additionally, CPT code C9734 does not include stereotactic navigation and frame placement, which means navigation platforms that help to determine a physical trajectory for either an incision or implant placement does not appear to be reimbursable under this code. The CPT code 0398T does include stereotactic navigation and frame placement with an additional focus for an intracranial movement disorder. Tremor dominant PD would be considered a movement disorder that this CPT code would cover as this has been approved for reimbursement purposes (CMS, 2023). The descriptions of these CPT codes appear to be straightforward, however, insurance companies create stipulations around reimbursement for these codes based upon a number of variables, which can include FDA clearance and the relevant trends outlined by the Centers for Medicare and Medicaid Services. This means that one may find value to implement these types of procedures into practice, however, if the procedure does not meet the requirements set forth by the organizations that reimburse for these codes, then the procedure may not be covered, which means the physician and the affiliated hospital may not be paid for their services.

This dilemma becomes an issue when patients 65 years or older that rely on healthcare associated government funds to receive treatment are denied due to procedural costs that may not be covered. Table 1 shows the estimated proposed payout for CPT codes 0398T and C9374 at $11,534.07 and $12,630.52 respectively. These proposed payouts did not include an estimated 70% coverage from the American College of Radiology dataset. The 70% estimated coverage was calculated as a way to show what could potentially be covered by private insurers as seen in Figure 3. The cost for CPT codes 0398T and C9374 with the estimated 70% coverage drops the potential cost down to $3,460.22 and $3,789.16 correspondingly. The overall estimated costs for these procedures were not available through the FAIR Health Consumer site and could possibly be due to the fact that these procedures are still considered new and have not been fully vetted by private insurance companies.

Regardless of the lack of information around coverage for these CPT codes, the average costs of CPT codes 0398T and C9374 are still 67% less in cost compared to the CPT code 00024 for the invasive inpatient in-network procedure at $36,732 per day for a hospital stay in the region of New York. The CPT code 00024 may only be applicable to interventions like DBS for diseases with tremors that include a major device implant as outlined by the code description, but the point remains that there have been other non-invasive forms of treatment to accomplish similar results. Additionally, many patients prefer less invasive options for treatment and the FUS treatment approaches have also been shown to be just as effective for lesion ablation techniques (Krishna, et al. 2023; Hu, et al. 2023; Hosseini, et al. 2022; Baek, et al. 2022; Lu, et al. 2023). The less invasive FUS treatment options also reduce the risk for potential infection or hemorrhage (Hu, et

al. 2023). The potential treatment options that use FUS should be considered in relation to the costs of those procedures compared to the more invasive approaches, to shed light on ways that patient quality of life and economic burden can be more adequately addressed.

Aside from some of the more invasive treatment approaches seen with CPT code 00024, therapeutic interventions have also been implemented and explored to help patients manage their neurodegenerative disease symptoms. An important point to note relative to the therapeutic interventions remains centered around the fact that none of these therapeutic interventions are used to cure the disease, they are only used to treat or manage symptoms as outlined in Table 2 with information from the GoodRx site. Data was acquired from the GoodRx site, which helps individuals find the lowest possible cost of drugs (GoodRx, 2011-2024). This site tracks the costs of drugs across various conditions to help individuals find optimal prices with or without insurance (IBID). Examples of individual medications for each disease state relative to AD, PD, and ALS were acquired to demonstrate what the cost of some of these medications can be relative to the therapeutic intention. The ALS drug Exservan presented with a cost as low as $9,059 compared to the AD drug Leqembi around $2,453 and the PD drug Ongentys at about $651. The cost of these drugs can be variable based upon whether an individual has insurance or if these drugs have generic versions that may be more affordable.

Leqembi was chosen based upon a current FUS research study that used a drug called Aducanumab, which can be understood as another Aβ monoclonal antibody treatment that was used in conjunction with FUS for more effective blood brain barrier drug delivery (Rezai, et al. 2024). The name of the Aducanumab drug called Aduhelm

was also listed on the GoodRx site for as low as $819, but was stated in an article by the Alzheimer's Association that this drug will be discontinued in 2024, therefore this drug was not listed in Table 2 and the closest drug to Aduhelm that had similar indications for an Aβ monoclonal antibody treatment was Leqembi (Alzheimer's Association, 2024 & GoodRx, 2011-2024). Additionally, Ongentys was selected because this drug primarily remains prescribed for patients that are also prescribed Levodopa (GoodRx, 2011-2024). Levodopa has been shown to induce dyskinesia like symptoms and has also been argued that this therapeutic may not be an effective treatment long-term due to the Levadopa refractory that can happen as a result of this prescribed therapeutic intervention (Baek, et al. 2022; Nagaki, et al. 2023; Krishna, et al. 2023).

Current research shows how Levodopa intervention can be seen as a common therapeutic avenue for PD and therefore justifies the choice for Ongentys, which can be used in conjunction to those currently integrated with a Levodopa therapy (GoodRx, 2011-2024). The drug Exservan was chosen because this drug remains a form of Riluzole, a commonly prescribed drug for the treatment of ALS symptoms, except Exservan presents in a pouch or film form to help individuals that may be unable to swallow pills (Mitsubishi Tanabe America, 2023). Many individuals that suffer from ALS and the associated symptoms present with an inability to properly swallow (Kvam, et al. 2023). Exservan was chosen to represent a more patient-centric form of the medication Riluzole, based upon research that outlines how certain symptoms of ALS like swallowing, may impact one's ability to effectively take their prescribed medication, which can ultimately affect their overall disease management and quality of life (Kvam, et al. 2023 & Mitsubishi Tanabe America, 2023).

The rate at which these drugs must be prescribed and consumed by the patient was not addressed and could be an area for further exploration as the rate in which a patient may be required to take these drugs can have a significant impact on economic burden for both patients and caregivers. The amount of therapeutic supply that patients can receive based on the outlined prices can be seen in Table 2. One way that these drugs may be more effective overtime and administered at a reduced cost would be to potentially integrate these drug therapeutics in conjunction with FUS for more direct drug delivery through the blood brain barrier. A study completed by Shen, et al. looked at the use of FUS-MB and the drug Edaravone, used as a treatment for ALS (Shen, et al. 2023).

This study aimed to assess how well FUS-MB helped to facilitate uptake of the drug through the blood brain barrier (Shen, et al. 2023). This study used a gadolinium injection to assess how well the uptake of the Edaravone seated past the blood brain barrier on magnetic resonance images (IBID). The results showed that FUS-MB and Edaravone decreased rapidly in plasma, which aided towards direct tissue uptake and was found to be two-times greater in the motor cortex region of the mouse brain compared to the Edaravone only treatment group (IBID). This data validates the consideration for FUS integrated treatments with some of these potential therapeutics to determine whether this avenue of drug delivery may be more effective overtime. The implementation of more research that focuses on how these therapeutics may be combined with FUS interventions can potentially change the way in which these diseases are treated and reduce the economic burden associated with these diseases. There may be potential to reduce the amount of drug administered to patients given that researchers have found a direct route to cross the blood brain barrier (Rezai, et al. 2024 & Shen, et al. 2023). This type of

approach could then possibly make these therapeutics less expensive for patients due to a reduction in potential quantity needed for effective therapy.

A limitation to this study remains centered around the fact that specifics were not outlined for each drug relative to insurance coverage for both private and government programs. Future research should be completed to outline how the costs of these drugs vary for private and government insured programs in addition to how often these drugs need to be administered for the effective management of symptoms. The information relative to cost and quantity should be explored to obtain a more accurate representation of how the quantity and cost of these drugs affect the primary population of individuals affected by neurodegenerative disease in the 65+ age category (Skaria, A.P., 2022; Yang, et al. 2021; Berry, et al. 2023). This in turn can help to validate the data around the total economic burden for each neurodegenerative disease and combined with the research on FUS interventions can improve quality of life for patients with more effective treatment protocols.

The use of FUS for BBBO to drive more effective drug delivery through the blood brain barrier has been validated through various mouse and human studies for AD, PD, and ALS (Rezai, et al. 2024; Shen, et al. 2023; Gasca-Sales, et al. 2021). The data that supports the use of FUS for more effective BBBO in conjunction to the outlined description of therapeutic intervention for CPT code C9734, holds promise for future FUS combined drug delivery treatment methods. The CPT code C9734 describes how this code can be used for FUS therapeutic intervention in parallel with magnetic resonance guidance or MRgFUS as the approach (American College of Radiology, 2021).

Further clarification would need to be addressed based on whether CPT code C9734 covers therapeutic intervention relative to BBBO. The code description beings with a preliminary focus of FUS ablation followed by therapeutic intervention (American College of Radiology, 2021). The research that supports BBBO for more effective drug delivery has typically been associated with LIFU approaches, which may disqualify this code for reimbursement purposes given the initial prompt of FUS ablation, which typically remains performed at higher intensities, commonly referred to as HIFU (Baek, et al. 2022; Hosseini, et al. 2022; Hu, et al. 2023). Additionally, a study was completed by Gasca-Sales, et al. to determine the safety and feasibility of BBBO for Parkinson's Disease Dementia in 2021 and was identified as an in progress clinical trial (Gasca-Sales, et al. 2021). This can lead one to believe that the CPT codes for BBBO and drug treatment intervention may not be created just yet.

There can be benefit to the integration of these reimbursement codes and protocols relative to BBBO and drug treatment intervention because these methods may help to reduce the overall cost of neurodegenerative disease treatment and care due to a decrease in overall drug costs. More specifically, if codes can be established to allow for the use of FUS for BBBO to aid in more effective drug delivery, then patients may need to receive less doses of the drug overtime, which reduces the overall economic burden to manage these diseases. Additionally, the implementation of FUS in these neurodegenerative treatments has the potential to produce more effective patient outcomes, which therefore increases overall patient quality of life. Further research needs to be completed relative to what government healthcare funds like Medicare specifically cover for these types of FUS and drug therapeutic interventions in addition to the

stipulations or requirements that either qualify or disqualify an individual for potential coverage.

These costs for both invasive, non-invasive, and therapeutic treatments are still too high and not affordable for patients 65+ years of age given that more than half of all Medicare recipients in 2019 lived on incomes below $29,650 per person (Cabin, W., 2021). An AD patient that qualifies for Leqembi would pay an annual rate of $29,436 ($2,453 per month for 12 months) for the therapeutic intervention without any additional coverage, which equates to almost the entire income per person for more than half Medicare recipients in 2019 (IBID). The cost of Leqembi with a 70% coverage would still equate to around $8,830 per year, which many individuals still cannot afford. Stronger initiatives need to be established to not only provide more cost-effective treatment options for patients that suffer from neurodegenerative diseases, but also integrate preliminary measures to ensure these patients can be diagnosed earlier on in the disease process.

Conclusion

Neurodegenerative diseases hinder the quality of life and economic feasibility of patients and caregivers throughout the disease journey. More effective treatment methods must be considered and explored to reduce the burden these diseases have on patients and caregivers. Current diagnostic measures lack urgency in propelling earlier treatment interventions and the socioeconomic impact on optimal care continuum methods remains far from attainable. The integration of ultrasound as a diagnostic and treatment modality must continue to be explored as research supports the immense potential this can have on more effective patient outcomes. Early diagnosis leads to earlier treatment intervention, which results in more promising patient outcomes that can contribute to more favored quality of life and economic stability metrics overtime.

Patients and caregivers suffer from the lack of equitable care due to stringent policies that do not consider the advancements of current research relative to neurodegenerative diseases in a cost-effective manner. Policies must reflect current advancements in the diagnosis and treatment of neurodegenerative diseases to ensure patients and caregivers receive the most optimal support and care. The total economic burden relative to these diseases can be reduced if policy makers consider how these diagnostic protocols and treatment interventions can yield more manageable disease states for patients' overtime.

The implementation of ultrasound as a diagnostic and treatment modality for neurodegenerative diseases can aid in the facilitation of these initiatives, while also upholding humanistic and patient-centered standards. The prioritization of the distinct needs and experiences of individual patients, advances medical interventions for

neurodegenerative diseases to not only become more effective, but also allow for the full embodiment of the patient's journey through these unique aspects to enhance one's quality of life. The current unpredictability of these neurodegenerative diseases does not excuse a failed system's lack of consideration for equitable care and quality of life. Ultrasound applications for the diagnosis and treatment of neurodegenerative diseases must be considered in parallel with policy amendments that make these methods economically feasible, while upholding the highest standard of care for all patients and caregivers.

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