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# Screening Techniques for Alzheimer's Disease

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by

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Abstract

Alzheimer's disease is a neurodegenerative disease that affects more than 55 million Americans. By the year 2050, experts project this disease will have increased three fold. Many screening techniques have been investigated to detect this disease early and begin treatment to slow its progression. The purpose of this study was to explore which medical modalities are the most effective for screening of Alzheimer's disease. This literature review includes three databases, including PubMed, CINHAL, and Cochrane Database of Systematic Reviews. Topics that were researched include: cognitive screening tests, neuroimaging, laboratory diagnostic testing, DNA, and combined studies. Research was conducted from October 8, 2017 to January 3, 2018. All resources were published within the last ten years. Limitations and strengths were considered within each modality. In each category, the following were found to be the most effective in screening for Alzheimer's disease: cognitive screening tests: MOST and MoCA testing; neuroimaging: PET scanning; laboratory diagnostic testing: biomarkers; DNA: DNA methylation and APOE genotyping; and combined studies: PET scanning. This review demonstrates that there are many screening modalities available to providers. This allows providers to choose their screening technique based on their site's availability, provider preference, and cost.

*Keywords*: Alzheimer's Disease, Alzheimer's disease screening, cognitive screening tests, DNA, laboratory diagnostic studies, neuroimaging

# Screening Techniques for Alzheimer's Disease

Alzheimer's disease is defined as a chronic neurodegenerative disorder that is seen primarily in adults who are older than 65. It is characterized as "progressive development of cognitive dysfunction, psychiatric, and behavioral symptoms, and difficulty performing activities of daily living" (DynaMed Plus, 2017). It is estimated that 5.5 million Americans are affected by this disease today. By 2050, it is predicted that 16 million Americans will suffer from Alzheimer's disease (Alzheimer's Association, 2017). This large increase is likely due to the "baby boomers" entering into retirement age. Because of this disease's high prevalence, it has become a popular subject of study. As time has progressed, this disease has become better understood and treatments have been formulated to slow its progression. Currently, however, there is no cure for Alzheimer's disease and current treatment options have many side effects. Because of this, researchers have been searching for effective screening tools to aide in early detection. The hope with early detection is to give patients a better quality of life with the initiation of early treatment.

With this literature review, the focus is on these screening techniques and the research that has been conducted within the last ten years. With each research analysis, the research's strengths, weaknesses, and findings was compile into meaningful conclusions. This research will enable clinicians and medical facilities to be well versed in the various screening techniques available and be able to provide better care to their patients. As providers, it is imperative to be up to date on the latest research, as medicine is continually evolving. With continual research, there will be a day when the medical community will better understand this disease and be able to target its efforts towards eradication of the disease.

## Statement of the Problem

A key issue with researching Alzheimer's disease is its difficulty to diagnose. It is thought that the only sure way to diagnose a patient with Alzheimer's disease is through an atopy of their brain. This raises the question- if there is difficulty defining Alzheimer's disease in a living patient, how does one screening for this disease that may or may not be present in this individual? Without fulling understanding the disease, how can practitioners provide effective care and treatment? Continued research has aimed to answer these questions. This literature review investigates further into the screening techniques that are currently available. To date, there is no known screening test that has been shown to detect this disease with 100% accuracy.

## Research Questions

What are the most effective screening options in the detection of Alzheimer's disease?

What limitations exist in these screening techniques?

What are the benefits in the different screening techniques?

## Methods

In this review, three databases were searched, which included PubMed, CINAHL, and Cochrane Database of Systematic Reviews, from October 8, 2017 to January 3, 2018. These works included systematic reviews, meta-analysis, and randomized control trials. PubMed database was the primary resource for researching screening techniques of Alzheimer's disease. Subject headings included "Alzheimer disease"[Mesh], "Alzheimer's disease"[Mesh], and "Screening"[Mesh]. Keywords that were searched included: screening, cerebral spinal fluid, CSF, blood, biomarkers, APOE, apolipoprotein E, mini-cog, MMSE, imaging, neuroimaging, clock drawing, amyloid, and amyloid deposits. In the CINAHL searches, the subject heading of "Alzheimer's disease"[MH], "Blood/BL"[MH], Cerebrospinal fluid/CF[MH], and Radiography/RA[MH], were used. The Cochrane Systematic Review database was searched with

the keywords of Alzheimer's Disease, Alzheimer's disease screening, Alzheimer's disease PET scan. To further refine the search, "AND" and "OR" were used between subject headings. Inclusion criteria of this literature review included systemic reviews, meta-analyses, or randomized control trials. All works were also published within the last 10 years and written in the English language.

## Review of Literature

### Theme One: Cognitive Screening Tests

In theme one, cognitive screening tests, four studies were reviewed. Tests that were investigated within the different studies included: Memory Orientation Screening Tests (MOST), Mini-Cog Screening Test, Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and clock drawing test. Cognitive screening tests have historically been used in a clinic setting due to their availability, ease of test administration, and ability to be administered in a timely manner. This theme investigates which of these screening techniques are deemed the better modality for detection of Alzheimer's disease.

Researchers Clinosky and Clinosky (2010) investigated whether integration of 3-word recall, list memory, clock drawing, and time orientation into the MOST would be a more accurate means of screening for Alzheimer's disease compared to Mini-Cog screening test and the MMSE. There was a total of 1,752 patients involved in the research. Tests were analyzed based on their ability to detect dementia and severity. Additional calculations in this study included: retest reliabilities, completion likelihood, internal consistency, and time costs. The results of this study concluded that the MOST was significantly more sensitive when compared to the Mini-Cog or MMSE. It also better correlated to standardized memory tests and more consistent over time. It was two times more likely to identify mild dementia in comparison to the

MMSE. The MOST had a high test-retest reliability over brief intervals (mean=66 days and standard deviation=61.4). The MOST had a significantly higher test-retest reliability than Mini-Cog ($p= .04$) or the MMSE ($p= .03$) The researchers concluded that the MOST is more accurate in identification of dementia and classification of its severity. The MOST should be considered the screening technique of choice in a clinical setting (Clinosky & Clinosky, 2010).

The MOST proved to be superior when compared to other screening techniques that are being used in clinics. The MOST demonstrated that is both a better screening tool than the Mini-Cog and the MMSE, and that it had better reliability in a shorter period of time. The researchers of this study had declared that they had no conflict of interest when publishing their findings, and they had received no financial support with the production of this study as well. This is significant, for it demonstrates that there was no bias towards any of the screening techniques. The authors do state that there are several limitations that do exist, including the need for replication of their study. The authors also state that their data does not represent cognitively normal elderly population. With 95% of participants identifying as Caucasian, this study was not racially diverse. There is a Spanish version of the MOST that is in development. This indicates the poor diversity and results of this study and is less representative of an American clinic. However, the authors do state that the MOST components are common and should be universal among different racial backgrounds. There is some skepticism with this comment because American patients have both diverse racial and ethnic backgrounds with different biases and base knowledge. Would these results be reproduced in an African American population for example? Overall, this study is significant, but for the Caucasian patient population.

Freitas, Simoes, Alves, and Santana (2013) conducted a study to determine whether the Montreal Cognitive Assessment (MoCA) or the Mini-Mental State Examination (MMSE), was a

better screening tool for cognitive decline. They tested patients that have a mild cognitive impairment and those who were already diagnosed with Alzheimer's disease. One-hundred and eighty patients were included in the study. The patients in the study were divided into two groups: 90 patients with mild cognitive impairment and 90 that were diagnosed with Alzheimer's disease. Both groups took the MoCA and MMSE, and results were analyzed. The MoCA had a higher accuracy in differentiating patients that had mild cognitive impairment and those that were already diagnosed with Alzheimer's disease. The MoCA scored higher in specificity, sensitivity, positive and negative predictive value, and classification accuracy. In addition, the MoCA had a higher sensitivity when monitoring cognitive decline in patients over a long term period. This study concluded that the MoCA is a better screening cognitive tool than the MMSE and should be the cognitive screening of choice (Freitas, Simoes, Alves, & Santana, 2013).

This research is compelling and does demonstrate the power of the MoCA screening test for Alzheimer's disease, but several aspects need to be taken into consideration. Further research should be conducted due to the small patient population size. If this study was reproduced with a larger sample size it would demonstrate the true power the MoCA has over the MMSE. Due to the researchers analyzing only the amnestic subtype of mild cognitive impairment, this study may not represent all forms of cognitive impairment. They stated that conclusions made for other forms of mild cognitive impairment cannot be done accurately. This demonstrates that more research should be done to see how effective the MoCA is with the many other subtypes of mild cognitive impairment. Therefore, one inquires whether this data and results can be applied to the theme of screening of Alzheimer's disease. The authors also stated that they had a challenge in identifying patients with memory impairments, and those that that had other cognitive decline causes or psychological impairments. Being able to differentiate the cause in cognitive decline

brings about the different dilemma of whether the sample size was truly representative of someone with a mild cognitive impairment from this neurodegenerative disease.

This study demonstrated promising research for those with amnesic subtype of mild cognitive impairments. It validity, however, in screening for Alzheimer's disease should be questioned.

Nakashima et al. (2015) designed a study to find if there is a correlation between regional cerebral blood flow and types of errors on the Clock Drawing Test in Alzheimer's patients. There were 142 patients in this study. The criterion of inclusion into the study included: right handed (ambidextrous participants were not included), could not have current medical or psychiatric disorders, and did not have significant focal lesions found on MRI scan of the brain. All the participants were Japanese The participants underwent both a SPECT and neuropsychological testing with the time between the two tests being less than two months apart. The SPECT was used to measure the patient's regional cerebral blood flow. They used the Mendez scoring method to quantify their results. The results indicated that there was a positive correlation between regional cerebral blood flow in the left posterior middle temporal lobe and the total score on the clock drawing test. Furthermore, there were several other errors and blood flow relationships. Patients that did not point towards the number 2 or did not write the number 2, correlated with the left frontal lobe. Patients that had uneven number spacing showed a relationship in the bilateral frontal lobe. The deviation of the clock center showed a relationship with the left frontal lobe. If the patient had missing numbers, the regional blood flow was found to be in the right parietal lobe. If patient had uneven number distance of the edge, the right parietal/temporal lobe was found to correlate. If the patient drew same length of the clock's hands, there was bilateral temporal lobe correlation. Finally, if the patient did not close the circle of the clock, the left temporal lobe was seen to be the dominant lobe involved. Researchers

concluded that each error type on the clock drawing test correlated to a different brain region (Nakashima et al., 2015).

There were many strengths in this research. One aspect that demonstrated the power in the research was the fact that the authors compared their results to similar studies. The authors had concluded that the left posterior middle temporal lobe was positively correlated with a total score on the clock drawing test. It has been found that patients with left severe Alzheimer's disease had regional dysfunction in the left temporal cortex, which would affect their clock drawing test. This study also had limitations. The researchers did not assess if there was a correlation between the clock drawing test and other neuropsychological tests to the regional cerebral blood flow. The researchers also did not consider psychological impairments that could have influenced their results, such as depression. They also stated that their means of scoring, the Mendez method, is not a perfect scoring means to examine error types seen on the clock drawing test. All their patients were right handed. This is an interesting inclusion criterion. The authors did not establish their reasoning behind that inclusion standard. With all of the participants being Japanese, this makes one wonder whether the results would be reproducible in the United States. Would culture and language affect these results? Overall, this research is strong with their data and the data from other studies that were presented to further solidify their research. The limitations should be considered, especially their method of detecting errors. However, they used this method throughout their entire study, so there is consistency in their results.

Tan, Herrmann, Mainland, and Shaulman (2015), performed a review of MEDLINE, PsychINFO, and Embase to investigate clock drawing and its effectiveness in differentiating Alzheimer's from other dementias. Twenty studies were included in this review. The different dementias that were compared included: Alzheimer's disease, dementia with Lewy bodies,

frontotemporal dementia, vascular dementia, and Parkinson's disease dementia. Most of the studies did not find significant differences in qualitative clock-drawing test scores between the groups. However, there was differentiating scores when comparing patients with Alzheimer's disease and frontotemporal dementia. Patients that had frontotemporal dementia scored higher on clock drawing tests than the Alzheimer's disease patients. The review concluded that the clock-drawing test is useful for differentiating between Alzheimer's disease and frontotemporal dementia. It is, however, limited in its usefulness when differentiating between other dementias. It was suggested that doing a qualitative analysis on the type of clock-drawing test errors may be beneficial in being able to differentiate between the types of dementia (Tan, Herrmann, Mainland, & Shaulman, 2015).

This review demonstrated the strength and weakness of the clock drawing test as a means for differentiating dementia. Though it does prove to be effective in certain instances, it fails to show how providers could use this screening tests to determine whether a patient has Alzheimer's disease. One should question how these researchers established the different forms of dementia in the set of participants. Other limitations with this study that was discussed included the methodology, sample of participants, the way the clock drawing test was administration, and their scoring system. The authors did not receive any funding for their research. This may indicate the lack of bias towards results. However, the authors did not complete a conflict of interest disclosure. Why did the researchers not complete one? This research was an interesting use of the clock drawing as a means of screening, but should be questioned as to how they could define these different dementias types.

**Theme Two: Neuroimaging**

In theme two, neuroimaging, three studies were reviewed. Tests that were investigated within the different studies included: FDG PET, amyloid PIB PET, and dual biomarker C-PIB PET. Neuroimaging is not a typical first line means of investigation of Alzheimer's disease. Researchers, however, are enthusiastic about the potential that this modality holds. This theme investigates which of these neuroimaging techniques yields the highest potential in the detection of Alzheimer's disease.

Fu et al. (2014) compared the (18) F-FDG PET scanner and the "dual biomarker" (11) C-PIB PET [(11) C-pPIB and amyloid PIB ((11) C-aPIB)] for a screening of Alzheimer's disease, patients with mild cognitive impairment, and patients that were cognitively "normal". There were 40 participants in this study: 14 cognitive normal, 12 with mild cognitive impairment, 14 with Alzheimer's disease. All participants were scanned with the FDG-PET and dual biomarker scanner. Results of this study indicated that both the FDG and dual biomarker yielded similar radioactive distribution patterns. It was found that the FDG scanner performed better than the dual scanning in differentiating between Alzheimer's disease vs. mild cognitively impaired patients, and mild cognitively impaired patient vs. cognitively normal. However, the pPIB + aPIB and FDG + aPIB yielded the highest accuracy between Alzheimer's disease and cognitive impairment. The FDG + aPIB were the best screening for classifying mild cognitive impairment vs. cognitively normal. The researchers concluded that the dual biomarker PET scanning technique holds promise as a useful biomarker in measuring neural activity and may aide in detection of Alzheimer's disease (Fu et al., 2014).

This study was helpful in testing two promising neuroimaging techniques. However, there were several challenges that these researchers faced. They had difficulty classifying

patients into the three groups, especially those that were mildly cognitively impaired vs. cognitively normal. Because of this, they created a criterion to categorize the different patients. This categorization is helpful for this single study; however, it is not used universally amongst other neuroimaging studies of cognitive decline. The definition of "mild" is also an aspect to question. Would patients who are displaying beginning stages of Alzheimer's disease would be detected? Would they be considered "mild" enough according to these researcher's standards? This study also only focused on mild to moderate Alzheimer's disease. They did not discuss how patients with severe Alzheimer's disease would perform on these tests. There were only 40 participants in this study, indicating low generalizability. When discussing the inclusion process of this study, the authors stated that all their participants were right handed. This statement was odd and readers should wonder the significance of that. Would there be differences in patients who are left hand dominant? With the low number of patient participants and the limitations for classification, further research needs to be investigate for a solid conclusion to be made.

Rabinovici et al. (2011) compared PET scanning with amyloid ligand Pittsburgh compound B (PiB-PET) to flouorodeoxyglucose (FDG-PET) in discriminating between frontotemporal lobar degeneration and Alzheimer disease. There were 62 participants with Alzheimer's disease, and 45 participants with frontotemporal lobar degeneration. Both groups had PiB-PET and FDG-PET scans. The PiB scans were classified in two groups as positive or negative, and FDG-PET scans were rated visually and categorized as having Alzheimer's disease or frontotemporal lobar degeneration. Results from this study suggested that PiB-PET scans had a higher sensitivity for Alzheimer's disease when compared to FDG-PET. Both yielded comparable specificities. PiB-PET had a higher sensitivity and FDG-PET had a higher specificity, when classifying quantitatively. Therefore, it was concluded that both the PiB-PET

and FDG-PET scanning techniques were comparable in classifying a patient with Alzheimer's disease (Rabinovici et al., 2011).

The results of this study demonstrated the power that both neuroimaging techniques have in terms of classification of Alzheimer's disease. Depending on a facilities availability of techniques, this research proves that either would be sufficient. However, this study has limitations. There was a question whether these tests would be valid in a clinical setting with a patient that has a suspected cognitive impairment. Because it focused in patients with known Alzheimer's disease and frontotemporal dementia, it is limited to its use with those two diseases solely. We do not know the extent of their use in detection of other forms of cognitive impairment. The comparison between the PiB-PET and FDG-PET to patients with confirmed diagnosed Alzheimer's disease was also flawed. Only a small set of patients provided the histological confirmation of Alzheimer's disease. How could the researchers classify the other participants as patients with Alzheimer's disease? The study also used participants that were "younger", and stated their results may not be able to be applied to the general population or elderly. This is a red flag, for most patients with Alzheimer's disease are those who are elderly. Another issue that this study has was with one of the screening techniques. The amyloid PET scan is not able to differentiate between amyloid positive and amyloid negative diseases. This is an issue, for amyloid-positive can be found in patients with dementia with Lewy bodies, and amyloid-negative disease can be present in psychiatric diseases that can mimic frontotemporal lobar degeneration. This issue was not discussed in the study. MRI and FDG-PET scanning can differentiate between the amyloid-positive and amyloid-negative, therefore they may be considered superior screening advantages in that respect. In addition to the limitation of a small sample size, the participants were also recruited from the same dementia center. This specific

sample is narrowed in geographical and cultural settings, which may not represent the general population. This study does have valid content, but further investigation on these limitations should be considered.

Smailagic et al. (2015) investigated different studies regarding the accuracy of the F-FDG PET scan in identification of patients with mild cognitive impairment who would progress to Alzheimer's dementia or other types of dementia. The authors included 16 studies, which involved 697 patients with mild cognitive impairment. The study sizes in these studies ranged from 19 to 94. The youngest sample ranges in ages from 55 to 73 years old, and the oldest sample was 71 to 86 years old. The percentage of the participants in this study who eventually progressed to Alzheimer's disease ranged from 22% to 50%. The authors believed that these studies had unclear risk of bias because there was no concrete statement of how participants were selected and how the diagnosis of Alzheimer's was established. They also estimated that more than 50% of the studies had poor methodology. The authors concluded that the F-FDG PET scan as a single screening test, does not accurately classify patients with mild cognitive impairment and does not predict those who will develop Alzheimer's disease in the future. It is thought that for every 1000 F-FDG PET scans, 174 will have a negative scan, but will progress to Alzheimer's disease, and 285 scans that were positive will not progress to the disease. Therefore, it was stated that the F-FDG PET scan in patients with mild cognitive impairment is not able to predict whether they will develop Alzheimer's disease in the future (Smailagic et al., 2015).

This analysis demonstrates the limitations neuroimaging has as a screening tool of Alzheimer's disease. A strength this study did possess was that the authors believed this review encompassed most of the literature on this topic. This is difficult to know for a fact, but there is a solid foundation of research. Researchers, however, did state that analysis of the research needs

to looked at skeptically due to the potential bias that exists in the different studies. Limitations also exist with the clinical diagnosis of Alzheimer's disease or the other forms of dementia. Patients whose disease was established post-mortem was more conclusive than other diagnoses via PET imaging. How accurate was the diagnosis of Alzheimer's disease was in their participants? Further research needs to be conducted to see the validity of the results in this review. The biases and limitations that these studies possess needs to be taken into account.

**Theme Three: Laboratory Diagnostic Tests**

In theme three, laboratory diagnostic tests, four studies were reviewed. Tests that were investigated within the different studies included: beta-amyloid proteins, tau proteins, and biomarker proteins. This theme is a timely topic. For years, researchers have attempted to use laboratory studies as a means of identification of Alzheimer's disease. This theme investigates which of these tests has the highest potential in the detection of Alzheimer's disease.

Burnham et al. (2016) investigated whether high or low neocortical beta-amyloid proteins (NAB) could predict a patient's risk of development of Alzheimer's disease within a 54-month period. There were 585 healthy controls and 74 patients with mild cognitive impairment in this study. The patients were then divided into high or low NAB groups. At the 54-month recheck, the results of the study yielded 12% of healthy control patients with high NAB progressed to Alzheimer's disease, whereas 5% of the healthy controls with low NAB progressed to Alzheimer's disease. The patients had mild cognitive impairment found that 40% who had high NAB progressed to Alzheimer's disease, vs. only 5% that had low NAB. In conclusion, the authors stated that patients with higher NAB had faster rates of memory decline compared to those with low NAB. The researchers believe that the use of NAB could predict neurological decline (Burnham et al., 2016).

This study demonstrated how blood based analysis could be used to estimate the risk for development of Alzheimer's disease. However, there were some limitations with this research. The researchers were unsure if participants could physiologically change from the low to high NAB category within the 54-month time lag. Does NAB protein change from high to low throughout a patient's lifetime? How about during short 54-month period? The cognitively healthy controls were also not random. They were from a community that is well educated and scored high on cognitive test, which does not represent a typical American community. Another limitation with this study was the patients that were diagnosed with Alzheimer's disease was not conformed with histology, therefore the accuracy of their diagnosis is put into question.

Mattsson et al. (2016) designed a study to test whether there is a correlation between plasma tau and Alzheimer's disease. They gathered 179 patients diagnosed Alzheimer's disease, 195 with mild cognitive impairments, and 189 that were healthy controls from the Alzheimer's Disease Neuroimaging Initiative (ADNI). They did a cross-sectional analysis with 61 patients with Alzheimer's disease, 212 that had mild cognitive impairments, 174 participants that claimed to have cognitive decline, and 274 healthy controls from the Biomarkers for Identifying Neurodegenerative Disorders Early and Reliability (BioFINDER) in Sweden. They had a total of 1284 patient in this study. Testing techniques included: plasma tau, MRI, CSF biomarkers, and fluorodeoxyglucose-PET scanner, and cognition tests. The results of this study concluded that patients with Alzheimer's disease had a higher plasma tau, higher CSF tau, and lower CSF beta-amyloid proteins (A[beta]42). There were weak correlations that were detected between the ADNI and BioFINDER. A longitudinal analysis was done with the ADNI population, which showed associations between the plasma tau protein and patients that had worsening cognition, hypometabolism, and atrophy within the brain. The authors concluded that the plasma tau did

reflect changes in pathophysiology that are associated with Alzheimer's disease. However, there was also a large overlap between the normal aging process and patients with Alzheimer's disease. Therefore, the authors concluded that the plasma tau alone cannot be used as an Alzheimer's disease biomarker (Mattsson et al., 2016).

This study was strong with the number of participants that partook in this study. They were also able to compare two large groups to see if the results could be reproducible between them. However, it was shown that there was a weak correlation between the ADNI and BioFINDER. The BioFINDER and ADNI participants were handled with different protocols, and analyzed in different labs and kit lots. This may have contributed to the weak correlation between the two. There were also participants that had plasma tau below the lower limit of quantification in the lab. They were not excluded from the study because of potential bias. Because of this, there is no way to quantitatively measure these patients and therefore makes one question how they entered these patients into their calculations. Another limitation that the use of only one plasma tau assy. Other tau fragments may be a more accurate in representation of Alzheimer's disease pathophysiology. The researchers also did not consider the other comorbidities that may affect the tau protein. Could a patient's comorbidities be contributing to their neurodegenerative disease? Could comorbidities mask the impact the tau protein has on this disease? This research was also conducted in Sweden. Would environment, culture, and genetics influence the tau protein? This research did prove that there is some association between the tau protein and Alzheimer's disease, but further research needs to be done before using this protein as a means of screening for this neurodegenerative disease.

O'Bryant et al. (2011) designed a study to investigate the relationship between serum biomarker proteins and Alzheimer's disease. An analysis was done with 197 patients with

Alzheimer's disease, and 199 control patients that were from the Texas Alzheimer's Research Consortium (TARC). There was also an analysis with 112 patients diagnosed with Alzheimer's disease, and 52 control patients that were from the Alzheimer's Disease Neuroimaging Initiative (ADNI). A biomarker risk score, lab tests (homocysteine, total cholesterol, triglycerides, glucose), and the patient's demographics (gender, age, education, and APOE epslion4) were documented. Eleven proteins were identified having a correlation coefficient between plasma and serum. The proteins included, "C-reactive protein, adiponectin, pancreatic polypeptide, fatty acid binding protein, interleukin 18, beta 2 microglobulin, tenascin C, T lymphocyte secreted protein 1.309, factor VII, vascular cell adhesion molecule 1, and monocyte chemotactic protein 1." The researchers had concluded that the biomarker risk score when combined with the patient's demographics and lab data improved the accuracy of detection of Alzheimer's disease substantially. Researcher were able to create a model in the TARC patients, that was able to predict results of the ADNI analysis. The authors concluded that there are proteins in serum and plasma that are associated with Alzheimer's disease (O'Bryant et al., 2011).

This study was interesting because of the strong relationship between proteins identified and Alzheimer's disease. The authors had many ways in which they analyzed their data, which demonstrated the value of their data. Their data was also compared to that of large scale study, which yielded the same conclusions. The authors were able solidify their conclusion that there are blood-based tools can be used for Alzheimer's disease screening. Researchers were able to produce an algorithm can be made across serum and plasma. The language in their discussion made it appear as if they had created a novel idea and how superior their findings were to prove their hypothesis. They did not, however, discuss limitations or weaknesses that their study had. This is a red flag. Each study has limitations in their research that they could not overcome. One

should question the possible bias the authors had regarding these results. A similar study should be conducted to see if their results are reproducible. This research is promising, but other studies with a similar theme should be investigated.

Vemuri et al. (2017) identified 430 patients (age greater than 60) that were from the Mayo Clinic Study of Aging. Researchers wanted to investigate whether there is a correlation between patients with comorbidities and neurodegeneration. Participants underwent amyloid-PET, MRI, and Tau-PET scans on their brain. There were also 329 patients that underwent a FDG-PET scanning. The researchers established each patient's cardiovascular and metabolic conditions. This included: hypertension, diabetes mellitus, hyperlipidemia, cardiac-arrhythmias, stroke, and coronary artery disease. The results showed that participants who were positive for cardiovascular and metabolic conditions had a significantly greater neurodegeneration than participants that did not have those conditions. However, the two groups did not differ in the presence of amyloid or ERC-tau. A structural equation model that was created during this study, demonstrated that vascular health had a direct and indirect impact on neurodegeneration, but not on amyloid deposits. Participants with hyperlipidemia had a significant impact on ERC-tau. Therefore, authors concluded that vascular heath has a great impact on neurodegeneration in Alzheimer's disease, and not as much of an effect on amyloid deposition (Vemuri et al., 2017).

This article yields an stimulating correlation between vascular disease and neurodegeneration. This also showed that amyloid deposition may not be as accurate as a means for screening for Alzheimer's disease. Strengths that this study possessed was their availability to the patient's medical health records. This enabled the researchers to do a thorough evaluation of the patient's health conditions and create a strong correlation between their neurodegeneration and their health status. A limitation that this study had was that the researchers focused on

amyloid-sensitive tau protein. It is thought that this protein may be different in a patient with atypical Alzheimer's disease. Therefore, the tau protein may not be representative for Alzheimer's disease in its entirety. The researchers also looked at the data with a cross-sectional approach rather a longitudinal design to see if there were any casual associations that could be made between vascular health and blood serum biomarkers. Would the results have been similar if the researchers had analyzed the quantity and changes of amyloid deposition and tau protein concentration over a longer period of time? This study was well designed and did have many participants involved, demonstrating the strength of the research.

**Theme Four: DNA**

In theme four, DNA, two studies were reviewed. Tests that were investigated within the different studies included: DNA methylation and apolipoprotein E genotype. This is a relatively new idea and full of possibility as a means of screening. Since the 1970s, DNA sequencing has grown in popularity. The use of a person's DNA has opened many doors in the medical world. For example, there is now the ability to identify and quantify the chance of a person developing a disease, and even their treatment prognosis. Researchers are hopeful that they will be able to do the same with Alzheimer's disease. This theme investigates the potential DNA has in the detection of Alzheimer's disease.

Bollati et al. (2011) explored whether there is a relationship between DNA methylation and Alzheimer's disease. They used PCR to evaluate the methylation of SAT-alpha, LINE-1, and Alu sequences in 43 patients diagnosed with Alzheimer's disease and 38 patients that were considered cognitively "healthy." The researchers found that LINE-1 was increased in the patients with Alzheimer's disease when comparison to the healthy controls. Participants also underwent a Mini-Mental State Exam (MMSE). It was found that the participants that had the

best performance on the MMSE, also had a higher level of LINE-1 methylation compared to the other groups that scored poorly. The researchers concluded that DNA methylation may lead to further understanding of Alzheimer's disease and may be considered as a means of risk assessment (Bollati et al., 2011).

This information is solid in its findings. To truly understand the meaning of the research, methylation of DNA needs to be fully understood. DNA methylation is when a methyl group is added to the DNA. This can cause repression of gene transcription and expression of the gene (Jin, Li, & Robertson, 2011). Because LINE-1 DNA was linked to neurodegenerative decline, methylation of LINE-1 has the opposite effect. Patients with LINE-1 methylation would not be transcribing the gene and therefore performed better on the MMSE. There were, however, also some limitations to this study. First, they had a small sample size of patients, which begs to question the validity of the research. There is also the aspect of aging. It is thought that Alu methylation declines as patients age, and LINE-1 does not change overtime. This statement was based on a large study of elderly patients in Eastern Massachusetts. This is a bold statement to be made and makes a huge impact on the conclusion of this research. The natural aging process and the change in methylation should be investigated further. This is a compelling study, but cannot conclude with certainty the results because of its limitations.

Kennedy, Cutter, and Schneider (2014) tested the apolipoprotein E epsilon4 genotype as a means of inclusion or exclusion in clinical trials for Alzheimer's disease. The researchers took data from a meta-database of 19 studies and then created samples with APOE epsilon4 that ranged from 0% (those that are noncarriers) to 100% (all the carriers). The researchers then took the APOE epsilon4 carriers, and resampled them randomly. Participants that were APOE epsilon4 carriers had a slight increase in validity than compared to those that had the APOE

epsilon genotype only, or those with unknown APOE genotype. The results of this study demonstrated that participants that were APOE epsilon4 carriers have more cognitively impaired and had a faster decline. The researchers, however, did state that using this as an inclusion criterion, would not yield more efficient trials because less people would meet the inclusion criteria (Kennedy, Cutter, & Schneider, 2014).

This study displayed how the APOE epsilon4 gene correlated to cognitive decline. With analysis of its genotype, there appears to be potential as a screening means. This warrants further investigative studies. There are several limitations with this study has as well. First, the analysis of the APOE epsilon4 biomarker was the only biomarker that was researched. The researchers did not compare how one biomarker was more effective in screening than another. However, their focus was on this specific APOE subunit. There also is a limitation on how the primary analysis was conducted. The researchers grouped patients on whether they possessed the APOE epsilon4 or did not, and did not look at other genotypes. What their results would conclude if they were to consider the other genotypes? Further investigative research is warranted.

**Theme Five: Combined Studies**

In theme five, combined studies, two studies were reviewed. This theme was entitled combined studies due to there being several screening techniques that were incorporated into a single research study. This theme allowed for many techniques to be compared and contrasted to the earlier themes.

Bateman et al. (2012) performed a longitudinal study which analyzed 128 patients who underwent clinical and cognitive assessments, cerebrospinal fluid, blood tests, and brain imaging. The researchers used the patient's age at assessment as their baseline, and the patient's age when they started to display symptoms of Alzheimer's disease to calculate the estimated

time (years) from expected onset of symptoms. The researchers then did a cross-sectional analysis of the patient's baseline data in comparison to the estimated years from the expected onset. They were able to determine the severity of pathophysiological changes associated with this disease. The results varied according to different techniques analyzed. The concentrations of amyloid beta (Abeta) (42) in the cerebrospinal fluid showed a declined 25 years before the onset of symptoms. The PET scan using the Pittsburgh compound B could detect 15 years before onset of symptoms. The patients that had increased concentrations of the tau protein in the CSF showed an increase in brain atrophy that was detected 15 years before onset of symptoms. Impaired episodic memory and cerebral hypometabolism were seen 10 years before onset of symptoms. The Clinical Dementia Rating Scale and the Mini-Mental State Examination was only able to detect 5 years before onset of symptoms. Based on the results, the authors concluded that patients who had autosomal dominant Alzheimer's disease displayed many pathophysiological changes that occurred decades before the onset of symptoms. However, the authors stated that their conclusions were based solely on autosomal dominant Alzheimer's disease and could not be applied to sporadic Alzheimer's disease (Bateman et al., 2012).

This research is compelling, for it demonstrates many screening techniques that can predict the onset of symptoms many years before they were seen clinically. This research is strong in being able to document changes that occurred within these participants over 40 years. This is a powerful aspect, since researchers could be intimately involved in the changes the patients were undergoing towards their development of this neurodegenerative disease. This study was also published in 2012, demonstrating its timeliness. However, there are several limitations. First, the research was focused on autosomal dominant Alzheimer's disease. They did attempt to integrate results in their summary with sporadic Alzheimer's disease by

mentioning results from other studies, but one should question the validity and reliability in those studies to be able to integrate their results with the results of others. The results are also based on the cross-sectional data analyzed by the researchers, rather than longitudinal changes. How are the results influenced when converting from longitudinal results to that of a cross-sectional? There was not a secondary trial done to reproduce these results. It was suggested by researchers to have others try to reproduce their findings. Would others yield similar results with a completely different patient population and the patients from different generations? With this statement, it indicates some publication bias. Publishers would not attempt to publish a study just to reproduce an earlier study. With the increase in medical technology, would patient samples in younger generations demonstrate physiological changes differently due to screening proficiency or medical advancements? This study is a good addition to this review, and with other research backing these results, it will be strengthened.

Palmqvist et al. (2015) compared the accuracy of CSF biomarkers to amyloid PET scanning in diagnosing early-stage Alzheimer's disease. This was a longitudinal BioFINDER study of 122 healthy elderly patients, and 34 patients that had mild cognitive impairment, who had developed Alzheimer's disease within three years of this study. The researchers analyzed beta-amyloid deposits in nine regions of the brain with 18F-flutemetamol PET scanner. Cerebrospinal fluid was also analyzed with INNOTEST and EUROIMMUN ELISAs. The results that were obtained, could be replicated in 146 control participants and 64 patients that had mild-cognitive impairment or Alzheimer's disease. The overall conclusion of this study stated that the CSF biomarkers and amyloid PET could identify early Alzheimer's disease with high accuracy, but there was no difference in improvement in screening when combined. Therefore, the choice

of one screening tool over the other should be based on the site's availability, cost for the patient, and the providers preference of imaging (Palmqvist, et al., 2015).

This information demonstrates that we currently have two adequate screening techniques available to providers for screening of Alzheimer's in a patient. It also was published in 2015, indicating its relevance. In addition to its results, the study went into detail about pros and cons of the different techniques. This information is important to keep in mind when considering the best screening technique that is suitable for each individual patient. There is a limitation with this study, being that it had small sample size of participants. This study had powerful results that should be reproduced to demonstrate if all these screening techniques are truly as effective as the authors are stating. The researcher did not discuss limitations with this study. This is a red flag because each study has its limitations, and should be addressed to be a complete research analysis. If the research can be validated with other studies with similar conclusions, it would aide in strengthening the findings of this study.

## Discussion

This project has demonstrated the many techniques that are available as a screening means for Alzheimer's disease. Each modality has their own strengths and weakness that should to be considered for each individual patient. Within each theme, the most effective screening tool was deduced based on the above research.

In theme one, cognitive tests, Clinosky and Clinosky (2010) research, indicated that the MOST test yielded superior to both the Mini-Cog and the Mini Mental State Exam for its sensitivity and better correlation with memory test consistency over time. It also was able to detect mild dementia better than the MMSE. With Freitas, Simoes, Alves, and Santana (2013) research, they concluded that the MoCA was superior over the MMSE. It had higher specificity,

sensitivity, positive and negative predictive value, and classification accuracy. Because both tests were found to be powerful screening tools, providers are able to choose their tool based on site availability, cost, and provider preference.

To further expand on theme one, the clock drawing test was considered as well. Researchers Nakashima et al. (2015) were able to find a correlation between cerebral blood flow and clock drawing errors in patients that were diagnosed with Alzheimer's disease. Tan, Herrmann, Mainland, and Shaulman (2015) proved that clock drawing tests were able to differentiate between Alzheimer's disease and frontotemporal dementia. Both clock drawing tests demonstrated the relationship clock drawing has to Alzheimer's disease, however they did not indicate how clock drawing tests can be used as a sole means of screening. Both forms of research incorporated patients that were already diagnosed with Alzheimer's disease. They did not search to use clocking drawing test to differentiate between a healthy cognitive patient from a patient with neurodegenerative cognition. Therefore, based on the research that was present in theme one, the MOST and the MoCA should be used as cognitive screening tests for Alzheimer's disease in a clinical setting.

When considering theme two, neuroimaging, several conclusions were made by researchers. Fu et al. (2014) compared FDG PET and dual biomarker C-PIB PET scanning as a means for screening for Alzheimer's disease. Their results indicated that a combination of the tests yielded the best results. pPIB + aPIB and FDG + aPIB were able to accurately differentiate between Alzheimer's disease and cognitive impairment. The FDG + aPIB was able to classify patients into mild cognitive impairment and cognitively normal. Rabinovici et al. (2011) challenged these modalities and compared the amyloid PIB PET to the FDG-PET to see which was better at discrimination between a patient with Alzheimer's disease and frontotemporal lobar

degeneration. Both the PIB and FDG were considered to be comparable for classifying Alzheimer's disease. Finally, Smailagic, et al. (2015) went one step further to see if the FDG PET scanning would be able to identify whether patients that have mild cognitive impairment would progress to Alzheimer's disease or other forms of dementia. They concluded that FDG PET scanner could not predict whether a patient would develop Alzheimer's disease in the future.

Based on this research a few conclusions can be made. First, dual screening PET scanning (PIB and FDG) has potential as a means of screening in the future for Alzheimer's disease. Second, PIB and FDG is able to detect Alzheimer's disease comparably, and either can be used based on a facility's availability. Even with the detection of cognitive impairment, however, the FDG cannot predict whether a patient will progress to Alzheimer's disease. This research indicates the potential use of neuroimaging as a screening technique and is a promising modality with the use of PIB or FDG.

When analyzing the research in theme three, laboratory diagnostic tests, there appears to be inconsistent conclusions being made regarding beta-amyloid proteins, tau proteins, and biomarker proteins, in regards to Alzheimer's disease. Burnham et al. (2016) researched whether high or low neocortical beta-amyloid (NAB) would predict a patient's risk of development of Alzheimer's disease. They concluded that patients that had higher NAB had faster rates of memory decline than the patients with lower NAD. Mattsson et al. (2016) research went another step further and research both beta-amyloid proteins and plasma tau proteins. They found that patients that were diagnosed with Alzheimer's disease had higher plasma tau, higher CSF tau, and lower CSF beta-amyloid proteins. Vemuri, et al. (2017) approached their research considering the amyloid and tau protein presence in neurodegeneration, but also evaluated the

patient's vascular health. They found that patients that had cardiovascular and metabolic conditions had higher neurodegeneration compared to healthy patients. It was found that amyloid or tau proteins did not differ between the two groups (those with and without comorbidities). They concluded that vascular health had a direct and indirect impact on neurodegeneration, and had no effect of amyloid deposition. They also stated that to some extent, tau protein is linked to hyperlipidemia. However, this relationship needs to be investigate further according to the researchers. This research indicated that patients that displayed neurodegeneration did not differ in the amyloid or tau proteins when compared to those that with neurologically healthy. This research contradicts that of Burnham et al. (2016) and Mattsson et al. (2016). Based on the data presented, clinicians should be cautious with the use of these modalities as a means for screening for Alzheimer's disease.

Continuing with theme three, O'Bryant et al. (2011) investigated serum biomarker proteins and their relationship to Alzheimer's disease. They were able to correlate eleven proteins to this neurodegenerative disease in the patient's serum and plasma. The proteins included, "C-reactive protein, adiponectin, pancreatic polypeptide, fatty acid binding protein, interleukin 18, beta 2 microglobulin, tenascin C, T lymphocyte secreted protein 1.309, factor VII, vascular cell adhesion molecule 1, and monocyte chemotactic protein 1." The researchers combined the patient's demographics and lab data to improve the diagnosis of Alzheimer's disease. They were able to develop a model that could predict results of patients of another group. This is interesting research, however there are a couple aspects that need to be considered. First, clinically many laboratories may not be able test for these specific proteins and would need to send them out to other facilities, increasing the cost for the patient. Second, this model that the researchers had developed needs to be further investigated with patients with diverse

backgrounds to represent the American population. There is promise with the use of these biomarkers, but further research needs to be conducted.

In theme four, DNA, methylation and apolipoprotein E genotype was investigated. Bollati et al. (2011) found that patients that had higher levels of LINE-1 methylation performed better on the Mini-Mental State Exam. Researchers concluded that there may be a link between DNA methylation and Alzheimer's disease and should be considered as a screening tool for risk assessment. Kennedy, Cutter, and Schneider (2014) approached the link of DNA to Alzheimer's disease in a different direction, with analyzing the apolipoprotein E epsilon4 genotype. They were able to conclude that patients that were APOE epsilon4 carriers had more cognitive impairment and faster decline than those that had the APOE epsilon genotype only. Both studies had their limitations and further research should be conducted on both. However, this does demonstrate the potential that DNA in the screening of Alzheimer's disease.

The final theme, combined studies, both challenged and solidified results from above themes. Bateman et al. (2012) investigated beta-amyloid CSF, PET scanning, tau proteins in CSF, and Mini-Mental State Examination as a means for screening of Alzheimer's disease. They found that the concentrations of the beta-amyloid in CSF declined 25 years before the onset of symptoms. The researchers had hypothesized that Alzheimer's disease causes pathophysiological changes before patients begin to present symptoms. This is staggering data, however the use of beta-amyloid proteins as a screening technique has found to be questionable, as shown in theme three. Further research should be conducted regarding the validity that beta-amyloid has as a screening mechanism for Alzheimer's disease.

Continuing with theme five, Palmqvist et al. (2015) investigated CSF biomarkers to amyloid PET scanning for early diagnosis of Alzheimer's disease. They found that both CSF

biomarkers and amyloid PET scanning could be used in the identification of early Alzheimer's disease. Biomarkers were found the be effective screening tools according to the research in theme three. However, O'Bryant et al. (2011) investigated the biomarkers in serum, versus the medium of CSF in this research. The use of medium may not affect the validity of the biomarkers in detection of Alzheimer's disease. Further research needs to be considered. With the positive results of the PET scanning in this research, it further solidifies the use of neuroimaging as a screening technique, as seen in theme two.

This research presents how different modalities can be used as screening technique for Alzheimer's disease. With each modality, clinicians should keep in mind the strengths and weaknesses each possesses. With this project there are limitations as well. While there were many different sources included in this study, one cannot make conclusions solely on this research. This project was designed to present the research in a meaningful way and make inferences based on the studies. Second, the research did not include in depth statistical analysis of each study's statistics. Many studies can directly or indirectly sway readers to appear as if their data was statistically significant, but with further analysis, shows lack thereof. Throughout this process, particular attention was applied to any statistical flaws that presented as red flags. Finally, further research needs to be conducted on this topic. The research that was included in this work were published within the last ten years, and more research is continuing to be conducted on this topic. This is a relevant subject and one can predict that research will continue to grow and make solid conclusions on the best screening techniques.

## Applicability to Clinical Practice

Because of the increase in patients presenting with signs of Alzheimer's disease, the need for effective screening techniques has never been so prevalent. This project demonstrates the different medical modalities that can be used for screening of Alzheimer's disease both in rural and urban communities. Due to the vast array of choices for screening, providers are able to choose which modality to use based on site's availability, provider preference, and cost. For example, cognitive screening tests may be more applicable to a rural setting than neuroimaging due to availability. This literature review demonstrates that rural patients can receive just as effective screening when compared to those in an urban setting using more advanced techniques.

Time is another factor that should be considered. Each screening test varies in the time it takes undergo the study, and the time it takes to obtain results. Cognitive screening tests would be considered the fastest of the screening techniques discussed. It is, however, patient dependent and some patients may complete the study faster than others. The scoring is done by the clinician and immediate results are obtained. Diagnostic laboratory studies and DNA may or may not be send outs to other facilities. This takes additional time to send, complete the analysis, and finally obtain the results. Neuroimaging does require patient time and a trained professional to undergo the scans. Once the scans are obtained, a radiologist will be able to perform the analysis and declare the results.

Clinicians should be well-versed on the screening techniques that they have available and be able to interrupt the results. With continuing research, researchers will be able to utilize multiple means of screening that are effective and will accurately diagnose patients with this neurodegenerative disease. With early detection of this disease, implementation of treatments can begin and slow the disease progression.

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