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Use of the Montreal Cognitive Assessment as an Early Indicator of Tumor Progression in Patient with Stage III and IV Gliomas

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in Patients with Stage III and IV Gliomas

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Dedication

I dedicate this thesis to my beautiful wife Darla and my adorable infant daughter Brooklyn. In addition to the love and support they continuously and selflessly provide me each and every day, both have sacrificed a great deal to allow me the opportunity to fulfill my dream of achieving a master's degree.

My daughter has unknowingly forfeited treasured Daddy time. This has been an unfortunate repercussion of taking on such a difficult and time consuming task while starting a family. I'm sure when Brooklyn is older, she will understand, but it doesn't make it any easier. I thank you, my beloved Brooklyn and hope someday this accomplishment inspires you to fulfill your dream.

My wife has wittingly and willingly given up countless hours of precious time with her husband in support of my goal. Darla has sacrificed some of the finer things in life to accommodate the expenses of tuition. On plenty of instances she has performed double duty in taking care of the burdens that come with home ownership, just to allow me a few extra hours of peace and quiet to dedicate to my thesis. Although everything she has done for me during this journey is appreciated, her ability to be a supermom, taking on twice the parenting responsibility at times is what is most impressive and meaningful to me because Darla does her very best to make sure Brooklyn doesn't feel the absence of Daddy. I thank you, Darla for all you do and I love you with all my heart. I hope someday I am able to make it up to you.

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In addition to the committee members above, one other individual who played a crucial part in the development of this thesis was Jessi Parker. Jessi's statistical expertise was essential in the planning and execution of our research. Her involvement has greatly enhanced the composition of this literary work and was done gratuitously. I am very appreciative of her contribution and I hope, she as well, is pleased with our finished product.

Abstract

Patients diagnosed with high grade glioma have a short life expectancy due to rapid progression of disease following and/or during treatment. Magnetic resonance imaging (MRI) is the primary method of surveying tumor progression, but is costly, lengthy in duration and often uncomfortable for the patient. An alternative to MRI that is cost efficient and patient friendly is of great interest to the medical community. If this alternative could also provide advanced notification of disease progression, then this patient population would have the opportunity for earlier treatment and the potential for greater efficacy. To pursue this concept, we assessed whether the Montreal Cognitive Assessment (MoCA) could be that MRI alternative, potentially providing an early identifier of disease progression for the high grade glioma population. We retrospectively assessed a variety of medical and surgical data points, in conjunction with the MoCA scores for individuals with a high grade glioma diagnosis who received surgery and/or biopsy with radiation treatment and had at least one instance of disease progression. Of the 128 subjects intended to fulfill our sample size requirement, only 5 subjects qualified for enrollment. Our statistical tests were greatly impacted by this unfortunate circumstance and because of this we were not able to support the MoCA as hypothesized because the results did not reach the level of statistical significance. We have identified many interesting trends, but without an appropriate sample size these cannot be validated. We hope the study concept and design will provide the basis for future research that can build upon our hypothesis and provide a definite answer.

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Abbreviations

ALS   Amyotrophic Lateral Sclerosis

CT   Computerized Tomography

EMR   Electronic Medical Record

GPCOG   General Practitioner Assessment of Cognition

GVSU   Grand Valley State University

HIPAA   Health Insurance Portability and Accountability Act

IRB   Institutional Review Board

IS   Informational Services

MIS   Memory Impairment Screen

MMSE   Mini-Mental State Exam

MoCA   Montreal Cognitive Assessment

MoCA-MIS   Montreal Cognitive Assessment Memory Index Score

MRI   Magnetic Resonance Imaging

PHQ-9   Patient Health Questionnaire 9

REDCap   Research Electronic Data Capture

SAS   Statistical Analysis System

VIPR   Virtual Integrated Patient Record

WHO   World Health Organization

Chapter 1 Introduction

Introduction

High grade glioma is one of the most aggressive forms of brain cancer. Glioma refers to any tumor that is derived from a cell type within the brain known as a glial cell. Glial cells are the most bountiful cell type within the central nervous system. They surround, insulate and provide support to neurons, the basic unit of the brain. The abnormal growth of these cells can lead to the formation of gliomas, some being benign and others malignant. The most severe forms of the malignant glioma, that also pose the most significant threat, are called high grade. Within the United States, the annual incidence of new high grade glioma diagnoses is 14,000, which is roughly 5 cases per 100,000 people (1). High grade glioma patients have a very poor prognosis, and those with the most common type of high grade glioma, a glioblastoma, have a median survival time of only 14.6 months even with standard treatment (2).

The troubling reality with regard to treatment options for high grade glioma patients is that it is lagging behind many other areas of oncology due to the delicate and complex nature of the brain. Current standard of care involves maximally safe surgical resection followed by radiation and chemotherapy. These modalities have limitations in the brain, which present unique challenges related to morbidity associated with brain surgery and altered brain penetration of chemotherapeutic agents due to the blood brain barrier. Currently, there are many clinical trials researching alternative, more efficacious treatments.

The typical first step in therapy following diagnosis is to surgically remove as much tumor as feasibly possible without damaging the healthy brain. This would be followed by post-operative radiographic imaging, typically a magnetic resonance imaging (MRI) scan of the brain to serve as a baseline for future imaging comparisons. This is typically performed within 72 hours of surgery to best determine the extent of resection. Radiation begins 4 weeks after resection, delivering 60 cGy 5 days a week for 6 weeks. Repeat MRI of the brain is performed 3-4 weeks after completion of radiation for reassessment. Chemotherapy is typically given concurrently with radiation due to its ability to provide radio-sensitization. Adjuvant chemotherapy following completion of radiation is often offered as well. Despite this treatment, high grade gliomas are thought to be incurable tumors with the expectation of progressive disease at some point following treatment (3).

Ideally, early detection of tumor progression could allow for the ability to start treatment earlier, thus leading to greater efficacy and a potential delay or avoidance in quality of life decline. Surveillance is typically achieved through MRI scans as frequently as every 2-3 months. In rare instances where MRI may be contraindicated, computerized tomography (CT) scans may substitute as the medium for radiographic imaging. MRI comes with many inconveniences to the patient such as high cost, a somewhat lengthy appointment and discomfort brought on by loud noise and a confined space, so alternative surveillance methods would be a welcomed addition to the standard care for these patients.

Due to the fact that high grade gliomas wreak havoc on the control center of the human body, these patients can experience decline in many ways, but what is most noticeable, especially to close friends and family, is a decline in cognitive function. This can be a very disheartening thing to witness as it can deteriorate a person's mind to the point where a loved one can seem unrecognizable. Perhaps this symptom can be used to the patient's advantage in that cognitive function and its decline over time can be measured quantitatively through a variety of validated assessment tools. This raises the question of whether one of these cognitive assessment tools could be used to identify clinical progression in these high grade glioma patients.

One such tool with a great deal of potential due to its quick, easy and comprehensive nature is called the Montreal Cognitive Assessment (MoCA). The MoCA is routinely used in the neuro-oncology clinical setting at the Spectrum Health Brain and Spine Tumor Center in Grand Rapids, Michigan in an effort to quantify cognitive decline in patients with brain tumors. Because cognitive decline is a commonly known side effect of brain tumors such as high grade gliomas, utilizing metrics from these MoCAs may provide some insight on tumor progression.

Some very promising research was published in 2003 that investigated the use of a battery of cognitive assessment tools on 56 patients with recurrent brain tumors. The results demonstrated that a decline in brain function could be detected approximately 6 weeks prior to radiographic evidence of tumor progression in these patients (4). If the results of this study can be confirmed, then identifying and quantifying cognitive decline

in advance of tumor progression could be a huge step forward for the high grade glioma community. The battery of cognitive assessment tools used in this research did not include the MoCA nor has the MoCA been used in a fashion similar to the study's design, but if a comparable study focusing on high grade glioma patients were to display similar results using the MoCA, it may prove to be a reliable indicator of disease progression for this population with an abbreviated battery that is more quickly and easily administered.

Purpose

The purpose of this study is to evaluate whether the MoCA could be adopted as a reliable, early identifier of disease progression in the high grade glioma population and thereby limit the burden of radiographic imaging.

Specific Aim 1: Determine whether there is a statistically significant decline in MoCA scores from a predetermined baseline to disease progression.

Specific Aim 2: Determine the average time point between baseline and disease progression where MoCA scores see the largest magnitude of change between consecutive assessments.

Significance

If the anticipated outcomes of our research are confirmed and other future research within the neuro-oncology community validates our results, MoCAs could

become a universally accepted standard practice within neuro-oncology clinics around the country and possibly the world. At worst, in instances where radiographic evidence of disease progression is questionable, a MoCA would be able to provide a valid second method of diagnosis. More impressively, MoCAs have the potential to reduce the frequency of radiographic imaging and all the unfavorable consequences associated with radiographic imaging, such as time, expense, patient anxiety/discomfort and even radiation exposure when receiving a CT scan. If MoCAs do provide reliable early identification of high grade glioma disease progression, then the opportunity exists for physicians to provide early treatment. For a population with such a poor prognosis and limited quality of life, any advances in care would make a big difference when viewed from the patient's perspective.

Chapter 2 Review of Literature

Current Practices

Assessing patients for mild cognitive impairment is an elusive goal because there are no definitive diagnostic tests to objectively measure cognitive function. In addition, there is rarely a "normal" baseline measure of cognition available for a given patient that can be used in comparison with later assessments of cognitive function and potential decline. The current gold standard for diagnosis of cognitive impairment is the patient's clinical history, with corroboration from an informant. The clinician's collection of the patient's history and assessment should consistently use a combination of neuropsychological examinations, laboratory results (to exclude any other etiologies) and appropriate brain imaging (5). Although, neuropsychological testing alone cannot establish a diagnosis, it does contribute very useful information for quantifying cognitive decline. There is no single cognitive assessment tool recognized as the premier tool of choice, but the Alzheimer's Association does recommend the General Practitioner Assessment of Cognition (GPCOG), Mini-Cog and Memory Impairment Screen (MIS) based primarily on these tools' ease of use within the clinical setting and their equivalence or superiority to the commonly used Mini-Mental State Exam (MMSE) (6).

Clinicians typically prefer to use cognitive assessment tools that are short in length and easily administered within the office setting to not only examine cognitive deterioration over time, but also to identify whether a more comprehensive cognitive evaluation should be performed by a trained neuropsychologist. While conditions such as Alzheimer's, Parkinson's and dementia have the luxury of a slower rate of cognitive

decline during which changes can be assessed on a yearly basis, patients with an aggressive brain cancer can experience a much more rapid decline. Because of the progressive nature of brain cancers, progressing often over months, clinicians caring for these patients prefer a more frequent and less intense regimen of cognitive testing to accommodate a patient population that does not necessarily have time at its disposal.

Montreal Cognitive Assessment

The MoCA is a comprehensive cognitive screening test developed by Dr. Ziad Nasreddine, a neurologist who graduated from the University of Sherbrooke (Quebec) and completed his fellowship at the University of California, Los Angeles. Dr. Nasreddine's goal was to develop a quick, easy and comprehensive cognitive screening that is precise, specific and sensitive for use by clinicians of high volume, first line specialty clinics.

The MoCA was first validated in 2000 when it showed excellent performance in distinguishing between cognitively intact and impaired groups classified by a gold standard neuropsychological assessment (7). Another validation study occurred between 2003 and 2004, which confirmed the test's ability to distinguish normal controls from subjects with mild cognitive impairment or mild Alzheimer's disease (8). More recently, in 2010, a scoring system was created for the memory cueing section of the MoCA, which previously had only been assessed qualitatively (7). This new system is called the Montreal Cognitive Assessment Memory Index Score (MoCA-MIS) and it helps determine which subjects with mild cognitive impairment are most likely to

transition to dementia over a follow-up period averaging 18 months. Results of a 2013 study showed that mild cognitively impaired subjects with low MoCA and MoCA-MIS scores were more likely to show a rapid progression to Alzheimer's disease (9). With studies validating the impact of MoCA-MIS, it was eventually added to the MoCA as Version 8.1 (7).

Although Version 8.1 of the MoCA has been created, Version 7.1 is still widely used (see Appendix A for an example of MoCA Version 7.1). The MoCA has been translated and adapted for 46 different languages and dialects and is used in 100 different countries. It is even offered in alternative versions to minimize any learning effects from multiple assessments within a timeframe of 3 months or less (7).

The MoCA is divided up into 8 sections that are designed to activate a variety of the brain's cognitive domains. These sections are visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall and orientation. The visuospatial/executive section includes three exercises: an alternating trail-making test, a cube-copying test and a clock-drawing test. The alternating trail-making section reflects executive function and is designed to activate the frontal lobe of the brain, while the copying and drawing tests access visuoconstructional skills, thus stimulating both the parietal and occipital lobes. The naming section is a basic task that requires the test taker to identify and name 3 animals shown in pictures. This test stimulates the left hemisphere of the brain. The memory and delayed recall sections are intrinsically tied together. First, the test taker listens to a series of 5 words and is then asked to recall as

many as they can. This task is then repeated a second and third time, but on the third

trial the examiner delays recall of the 5 words until a later time. Finally, near the

conclusion of the assessment, the examiner asks the test taker to recall the 5 words

that were listed earlier, but without the list being read by the examiner prior to the recall.

Both the memory and delayed recall sections are designed to provoke the temporal lobe

of the brain. The attention section also includes three exercises: a digit span (forward

and backward), a vigilance task and a serial 7 subtraction test. In addition to attention,

these tests combine to also assess concentration and calculation, which localizes brain

activity to the frontal and left parietal lobes. The language section includes a sentence

repetition test and a verbal fluency test. These stimulate the left hemisphere of the

brain, but most commonly the left temporal lobe. The abstraction section uses a

similarities test where the examiner will ask the test taker to identify features that two

objects have in common. This type of test is designed to motivate the frontal lobe.

Lastly, the orientation section uses some basic awareness questions during which the

examiner may ask for the current date and time and/or the current location, arousing the

test taker's parietal and temporal lobes (10) (11). A general breakdown of cognitive

function and testing by location can be examined in Figure 1.

Summary of Cognitive Function & Testing by Localization
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FRONTAL **PARIETAL** **TEMPORAL** **OCCIPITAL**

Executive Function — Verbal fluency, Alternating sequences, Similarities, Go-no-go, Trails A & B

Behaviour — apathy, disinhibition

Sensory — neglect, graphesthesia, joint position, stereognosis, spatial orientation

Praxis — ideomotor (inf parietal lobule), dressing (right sup parietal lobule), constructional

Gerstmann's syndrome (angular & supramarginal gyri)

Topographic memory

Memory — orientation, word lists (CERAD, AVLT, BNS, MMSE, MIS), paragraph recall

Behaviour — Kluver-Bucy (b/l anterior tip; hyperoral, hypersexual, hypomobile, docile)

Naming — Boston naming test, Semantic fluency

Auditory — sound agnosia, phonagnosia, nonmelodious melody

Visual agnosia
Achromatopsia

Behaviour — Anton's syndrome

Attention — serial subtractions, WORLD, letter cancellation, digit span

Facial Recognition (R>L, lingual & fusiform gyri) — Famous faces

Visuospatial — cube, Rey-O, Line bisection, Balint's syndrome (b/l; simultanagnosia, optic ataxia, ocular apraxia), Visual agnosia

Praxis (lt hm)

Motor control — pantomime

Sensory processing — imitation

Object knowledge — object use

Visual processing — gesture recognition

Language (lt hm)

Transcortical motor aphasia | Broca's aphasia | Conduction aphasia | Wernicke's aphasia | Transcortical sensory aphasia | Semantic aphasia | Primary progressive aphasia | Alexia without agraphia

— fluency — repetition — comprehension — reading — writing

Figure 1. Visual categorization of cognitive function and testing by brain location (11).

The time required to administer the MoCA is roughly 10 minutes and is scored on a scale from 0 to 30 points. Scores of 26 and above are considered normal (12). Although research standards have not been established for severity levels, the "Frequently Asked Questions" page of the official MoCA website refers to scores of 18-26 as indicative of mild cognitive impairment, 10-17 as moderate and anything less than 10 as indicative of severe cognitive impairment (13).

Because cognitive dysfunction has been associated with many neurological and systemic diseases, the MoCA has been beneficial for detecting mild cognitive

impairment in a diverse array of conditions such as Alzheimer's disease, Huntington's disease, Parkinson's disease, fronto-temporal dementia, amyotrophic lateral sclerosis (ALS) and brain tumors, among others (7). One particular brain tumor that has not been explored in much depth with regard to the MoCA is the glioma. Gliomas represent 25% of all primary brain tumors (originating in the brain) and 75% of all those malignant, thus the MoCA utilized in this population could be quite impactful (14).

Gliomas

The word glioma is a general term that refers to all tumors arising from glial cells, a supportive tissue of the brain. Gliomas are classified by location, cell type and grade. Location is categorized as supratentorium, infratentorium, brainstem or spinal cord. The dividing boundary within the brain is a membrane known as the tentorium. Above this membrane is the cerebrum and below is the cerebellum and brainstem. Approximately 70% of adult tumors originate in the cerebrum and 70% of child tumors originate in the cerebellum (15). A much less common location, the brainstem, accounts for only 1-2% of adult gliomas (16). In contrast, the brainstem accounts for a much more prevalent 10-20% of gliomas in children (17).

Gliomas can also be classified by cell type. Within this classification system, the three main types are astrocytoma, oligodendroglioma and ependymoma, derived from the three types of glial cells that can form tumors: astrocytes, oligodendrocytes and ependymal cells, respectively. It is also possible for tumors to display a mixture of these cell types in what are known as mixed gliomas or oligoastrocytomas. Three other

variations usually included in this classification system, but not necessarily confined to one particular cell type are brainstem gliomas, optic gliomas and gliomatosis cerebri (18). Brainstem glioma cell types are not typically specified because of the limitations of obtaining tissue from this location; optic gliomas are thought to be astrocytomas and gliomatosis cerebri is thought to be an astrocytic process. With regard to their impact on cognitive decline, the cell type carries less weight when compared to the location of the tumor and degree of infiltration.

The World Health Organization (WHO) also classifies gliomas and other brain tumors by grade. The tumor grades range from I to IV, where a higher grade indicates a more advanced disease state. Grade I tumors are typically non-cancerous, slow growing and are associated with long-term survival. Grade II tumors are relatively slow growing, demonstrate atypical cell morphology and may spread to normal brain tissue or recur as a higher grade tumor. Grade III tumors are malignant, actively producing abnormal cells and invading into normal tissue; they often recur as grade IV tumors. Grade IV tumors are malignant, fast growing, actively produce abnormal cells, easily spread to normal brain tissue and often form new blood vessels to maintain such rapid tumor growth. Areas of necrosis in the center of grade IV tumors reflect growth that is outpacing the tumor's blood supply (19). There are many factors contributing to the transition in grade level for these tumors, but to give a general idea of the rate of change, a grade II may take roughly 5-7 years to become a grade III, while a grade III may only take 2-3 years to convert to a grade IV.

Radiographic Surveillance

High grade gliomas, grades III and IV, are the most aggressive gliomas. Because they grow quickly, they can severely impact the rate of cognitive decline. Consequently, these gliomas require the most frequent surveillance. The standard medical imaging technique for identifying glioma disease progression is the use of MRI, which allows tumors as small as 1mm to be detected. CT is also utilized in acute assessments or when MRI is unavailable or contraindicated. MRI is a reliable and minimally invasive form of radiography that has been used for decades to diagnose and stage cancers, along with a wide range of other applications. For individuals diagnosed with a high grade glioma, MRIs can be performed as frequently as every two months per standard of care for tumor surveillance. It is crucial to compare multiple MRIs in order to identify tumor growth. Although MRIs have been proven to be a safe form of radiography (if proper procedures are followed), they are very expensive (costs for machine use, interpretation by the radiologist and subsequent follow-up with a physician post-imaging), time consuming and can be somewhat uncomfortable for patients due to the loud noise and confined space. In addition, MRIs are somewhat subjective because the results are contingent upon the reader's interpretation of the imaging. With regard to high grade gliomas, MRI results are not always definitive because the tumor infiltration can be at a microscopic level and below the sensitivity of the test. Consequently, patients can clinically deteriorate without a clear radiographic correlate that suggests tumor progression. Even treatment options such as the chemotherapy agent bevacizumab (Avastin) can alter an MRI interpretation due to substantially decreased contrast enhancement, which is typically abnormal in progression of high grade gliomas.

Unfortunately, this is currently the best method of surveillance until alternative non-invasive substitutes for diagnosis are developed and proven to be effective. As such, alternative assessment measures that are able to identify tumor progression and also minimize the number of MRIs patients receive would be highly beneficial.

Relevant Research

A recent study by Meyers and Hess examined the cognitive deterioration of patients with recurrent brain tumors and suggested that a pattern of measurable brain function decline occurred approximately 6 weeks earlier than radiographic evidence of tumor progression. Figure 2 displays this pattern very nicely in the form of an event chart. These results would suggest that the extent of time between instances of radiographic surveillance is at least partially responsible for the delay in detecting progression, although the remaining burden likely falls on the technical limitations of radiographic imaging. This study used a battery of standardized psychometric tests for assessing a broad range of cognitive function (4). The idea of using cognitive deterioration as a more sensitive indicator of disease progression is an area of great interest for the neuro-oncology community because earlier identification of tumor progression could make additional treatment options available at a potentially earlier time point. It is hypothesized that earlier intervention could lead to improved disease control, but this is not yet proven. Although, the MoCA was not one of the assessment measures used in the Meyers and Hess study, its sensitivity and proven ability to identify mild cognitive impairment makes it a promising assessment tool for use in patients with high grade glioma.
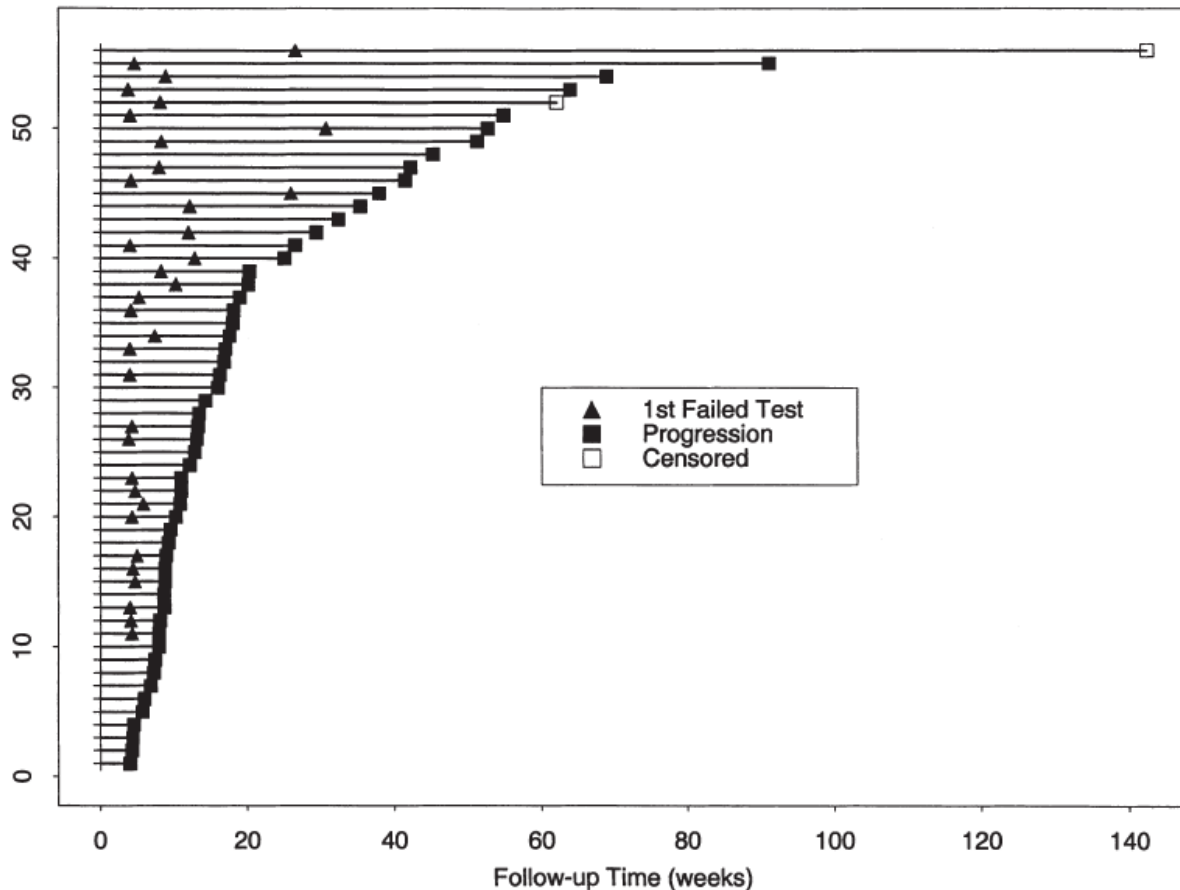
Figure 2. This event chart indicates the time between the first failed psychometric test and radiographic evidence of tumor progression for the 56 subjects who participated in this trial. The subjects marked as "censored" indicate those who had not yet progressed (4).

Research Site

The main campus of Spectrum Health, the largest medical center in West

Michigan, is located in downtown Grand Rapids and it has a very active neuro-oncology

multidisciplinary clinic known as the Spectrum Health Brain and Spine Tumor Center.

As in many other institutions, the physicians serving this facility already use MRIs

routinely to assess disease progression for high grade glioma patients. Interestingly

enough, one other evaluation tool that they use with this population is the MoCA. The

use of MoCAs was initiated in September of 2013 as a means to quantitatively measure

the cognitive decline observed in patients with brain tumors. It was selected as the

preferred psychometric test because it is quick, easy to administer, cost effective and

non-invasive. Since 2013, a large collection of MoCAs has accrued, providing readily

available data that can be compared with data from routine MRIs or the occasional CT.

This data was used to conduct a study evaluating whether MoCAs could be adopted as

a reliable, early identifier of high grade glioma progression. This would limit the burden

of radiographic imaging in the high grade glioma population and provide earlier options

for medical intervention to attempt to slow disease progression.

Chapter 3 Methodology

Research Preparation

In order to determine whether the sample size required for the study could be

supported by the patient population at Spectrum Health, a preliminary report was

executed in March of 2017 by Spectrum Health Information Services (IS) to provide a

general idea of the current patient population numbers at this institution. High grade

glioma diagnosis codes were used in combination with a date range dictated by the

initiation of the MoCA as a standard assessment in the Spectrum Health Brain and

Spine Tumor Center. As of the March 2017 report, it was estimated that 271 patients

had a moderately high potential of meeting the study criteria. Even after taking into

account that many potential subjects would screen fail following evaluation of all

eligibility criteria, we anticipated that the number of eligible subjects would still be

sufficient to achieve our goal of 128 enrolled subjects under a waiver of consent and

Health Insurance Portability and Accountability Act (HIPAA) authorization (see

Anticipated Statistical Analysis: Statistical Plan: Sample Size Determination).

Research Approval

A finalized research protocol was submitted to the Spectrum Health Institutional

Review Board (IRB) for review on July 27, 2017 and later approved on August 11, 2017.

Due to a reliance agreement in place between Spectrum Health and Grand Valley State

University (GVSU), a second review from GVSU's IRB was not necessary; however,

documents reviewed and approved by Spectrum Health were filed with GVSU's IRB and

a formal letter was received stating that GVSU would defer research oversight to

Spectrum Health's IRB. This letter was issued on August 25, 2017, giving final approval

to begin the research. The Spectrum Health and GVSU IRB letters can be found in

Appendix E.

Recruitment Methods

Following IRB approval, subjects were identified with the help of Spectrum

Health's honest broker program (an entity that has access to an entire data set and then

distributes portions of that data to those who should not have access to the entire data

set) in a similar fashion to how our preparatory report was generated. The honest broker

utilized the provided variables (age, diagnosis codes, date ranges, etc.) to flag potential

subjects, and their files were exported to a manageable list. Two additional strategies

were used to add a few extra potential subjects to this list. The first strategy was a

second report, built again by the honest broker program. This report was deemed to be

more robust in its search capabilities. It was able to specifically search for any MoCAs

documented in a certain area of the electronic medical record (EMR). Using this report,

we identified subjects with a high grade glioma diagnosis that had at least 3

documented MoCAs. This list was then cross referenced against the list provided by the

first report to identify any subjects that may have been missed. The second strategy

was to request access from the Spectrum Health IRB to utilize the screening log,

enrollment log and database from the Glioma Data Registry for Research (IRB#: 2016-

034), an approved research project being conducted at Spectrum Health. High grade

glioma subjects from the registry that had a known recurrence were also cross

referenced against the list provided by the initial screen to identify any more subjects

that were not identified previously. From there, the EMR from each individual subject on the list (325 total) was sequentially screened for eligibility.

Inclusion and Exclusion Criteria

The start date of the data collection window for this retrospective chart review was September 1, 2013, reflecting the approximate time when MoCAs were initiated into practice at the Spectrum Health Brain and Spine Tumor Center. The concluding date for the data collection window was August 11, 2017, the date of IRB approval of this research.

Inclusion Criteria

- Adults $\geq$ 18 years of age.

- Pathology diagnosis of a high grade glioma (WHO grade III or IV). Grade III pathologies included, but were not limited to, anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic mixed glioma (also referred to as anaplastic oligoastrocytoma). Grade IV pathologies included, but were not limited to, glioblastoma, gliosarcoma and gliomatosis cerebri.

- Surgical resection or biopsy of high grade glioma with post-op or post-biopsy radiation treatment.

- At least one instance of disease progression.

- Completion of a minimum of three MoCAs. The baseline MoCA subsequent to high grade glioma resection or biopsy with post-op or post-biopsy radiation, the

concluding MoCA (for purposes of this study) at the first instance of disease progression and a minimum of one MoCA in between.

Exclusion Criteria

- Individuals < 18 years of age at the time of high grade glioma pathology diagnosis.

- History of dementia.

Setting of the Research

The research consisted strictly of EMR data abstraction. The majority of data abstraction took place at the Spectrum Health Medical Center; however, approved mobile access to EMR software was utilized on occasion. There was no research interaction with any subjects because a waiver of consent and HIPAA authorization was granted.

Resources Utilized to Conduct this Research

For initial planning and final data analysis, we engaged the services of a Spectrum Health biostatistician. For recruitment purposes we accessed the Spectrum Health honest broker program. For screening purposes only, we used the screening log, enrollment log and database from the Glioma Data Registry for Research (details can be found under Methodology: Recruitment Methods). We also utilized Spectrum Health EMRs, specifically Epic and Cerner, which can be accessed anywhere on Spectrum Health campuses or via authorized mobile access. Other software programs such as OncoEMR/Virtual Integrated Patient Record (VIPR) and the Spectrum Health Cancer

Registry were listed in the protocol as potential resources for further medical information if needed, but were never used. Lastly, Research Electronic Data Capture (REDCap), a secure online database was chosen and operated as the depository of all data abstraction.

Procedures Involved in the Research

This retrospective chart review was initiated on August 25, 2017 following the receipt of GVSU's IRB deferral letter. It was conducted at Spectrum Health under a waiver of consent and HIPAA authorization. Research data collection took approximately 3.5 months, followed by an additional 2 months for data analysis. It is expected that the study will be closed with the IRB before its approved one-year duration is completed.

Once the research study was approved to proceed, potential subjects were identified with the help of the Spectrum Health honest broker program (see Methodology: Recruitment Methods). Each of the 325 identified potential subjects was individually screened for eligibility. This process involved reviewing each potential subject's EMR to confirm all eligibility criteria were met. The most efficient method for screening the list of potential subjects was to prioritize the search by using criteria that would exclude a subject. In this instance, the top two criteria that eliminated potential subjects were the requirements that subjects must have a history of completing at least 3 MoCAs and that they have a pathologic diagnosis of a high grade glioma. If potential subjects fulfilled these two requirements, a second tier of criteria were evaluated. This

included confirming that the potential subjects' MoCAs occurred at the time points required by the protocol (baseline, intervening and progression). This process of elimination continued until a subject met all criteria. At that point, the subject was considered enrolled in the study and was assigned a unique study identification number to maintain confidentiality. A study correlation tool was kept securely on Spectrum Health's network drive to link subjects to their study number.

For enrolled subjects, retrospective data was collected from the EMR systems available at Spectrum Health. All data was entered and stored in a secure online database (REDCap) that was only accessible by IRB approved personnel. The REDCap project created specifically for this study was titled 'ONC – MoCA Study' and contained a series of data collection instruments built to capture all relevant data (see Appendix B). Once the data from all enrolled subjects was collected and entered into REDCap, it was exported for the ensuing statistical analysis. In addition to carrying out our planned statistical analysis that addressed our specific aims and secondary objectives (see Methodology; Anticipated Statistical Analysis), we also utilized data from our screening log to summarize the patient population, including any reasons for screen failure. The goal of this additional information was to provide a macro view of the routine use of the MoCA and how it aligned with our initial expectations.

Anticipated Statistical Analysis

The following information is the proposed statistical plan that established the foundation for the design of this research study. This information is extremely important

because it is crucial to understanding how we planned to address our objectives and answer our research questions. As a disclaimer, many research projects do not progress as anticipated, even if planned out exceptionally well. This particular study, unfortunately fell into this group. What occurred and the factors that contributed to this will later be explained in more detail (see Results and Discussion), but for now, having a clear comprehension of our precursory research strategy is essential.

Statistical Plan

Data analysis would use Statistical Analysis System (SAS) Enterprise Guide Version 7.1 to provide summary statistics. Quantitative data would be expressed using means and standard deviations, while qualitative data would be expressed using frequency and percentages.

Primary Analysis. To test the difference in MoCA scores between baseline and disease progression as described in specific aim 1, we would use a parametric paired t-test since the outcome of the MoCA score is continuous and the pre and post scores are dependent observations. In essence, we would take the average value of all patients' baseline MoCA scores minus disease progression MoCA scores and compare that to zero. Then we would determine whether that difference was significant. A nonparametric Wilcoxon Signed Rank test was to be used if the assumption of normality was not met.

Determining the average time point between baseline and disease progression

where MoCA scores show the largest magnitude of change between consecutive assessments would be calculated using SAS as well, but would not require a statistical test. Rudimentary calculations proved sufficient for achieving the result. For each eligible subject, the date of the MoCA that occurred between baseline and disease progression with the greatest magnitude of change between consecutive assessments would be identified. This date would be subtracted from the date of disease progression and the resulting number of days would then be averaged across subjects. This would help quantify how much earlier, in days, disease progression could potentially be detected by a MoCA relative to radiographic imaging. There were, however, a few exceptions to the rule. Any subject that had an equal magnitude of change between all MoCA scores (steady slope) would be excluded from the sample used to calculate specific aim 2. When identifying the largest magnitude of change for each subject, only those changes where scores were declining would be acceptable. Lastly, when identifying the largest magnitude of change for a particular subject, there could be multiple occurrences between baseline and disease progression that were equal in magnitude and the largest. If this were the case, the date of the MoCA with the largest magnitude of change from its preceding MoCA and that is closest to baseline would be utilized for the data point for that particular subject.

Secondary Analysis. Additional statistical testing was planned for a variety of other demographic groupings of interest in order to identify confounding variables that could impact, positively or negatively, the difference in MoCA scores between baseline and disease progression. Distinguishing these factors could help identify demographic

groupings with higher possibilities of false positives/negatives affecting the reliability of the MoCA in early identification of disease progression. To test the average difference in MoCA scores between baseline and disease progression to determine whether there was a difference between demographic groupings, we would use a series of parametric two sample independent t-tests since the outcome of the difference in MoCA scores was continuous and the demographic groupings were all independent groups. Essentially, we wanted to compare two groups to see if there was a significant difference between them. If so, the variable would be a confounder. A nonparametric Wilcoxon Rank Sum test would be used if the assumption of normality was not met. The following is a list of the demographic groupings and how each variable was to be defined.

- Age: Subjects would be divided into two age groups. Those 18-59 years of age and those $\geq$ 60 years of age at disease progression.

- Tumor Grade: Subjects would be divided into two groups. Those who were diagnosed at resection or biopsy with a WHO grade III tumor and those who were diagnosed at resection or biopsy with a WHO grade IV tumor.

- Chemotherapy: Subjects would be divided into two groups. Those who were being treated with chemotherapy at the time of disease progression and those who were not being treated with chemotherapy at the time of disease progression. For purposes of this research study, chemotherapy is defined by the following medications: Temodar (temozolomide), Avastin (bevacizumab), Gleostine (formerly marketed as CeeNU) (lomustine), Opdivo (nivolumab), Keytruda (pembrolizumab), Paraplatin (carboplatin) and Camptosar (irinotecan).

- Stimulants: Subjects would be divided into two groups. Those who were being treated with stimulants at the time of disease progression and those who were not being treated with stimulants at the time of disease progression. For purposes of this research study, stimulants were defined by the following medications: Provigil (modafinil), Nuvigil (armodafinil), Ritalin (methylphenidate), Adderall (amphetamine/dextroamphetamine) and Vyvanse (lisdexamfetamine).

- Antidepressants: Subjects would be divided into two groups. Those who were being treated with antidepressants at the time of disease progression and those who were not being treated with antidepressants at the time of disease progression. For purposes of this research study, antidepressants were defined by the following medications: Lexapro (escitalopram), Prozac (fluoxetine), Celexa (citalopram), Cymbalta (duloxetine), Effexor (venlafaxine) and Zoloft (sertraline).

- Anti-Epileptic Drugs: Subjects would be divided into two groups. Those who were being treated with anti-epileptic drugs at the time of disease progression and those who were not being treated with anti-epileptic drugs at the time of disease progression. For purposes of this research study, anti-epileptic drugs were defined by the following medications: Keppra (levetiracetam), Vimpat (lacosamide), Lamictal (lamotrigine), Topamax (topiramate), Trileptal (oxcarbazepine), Tegretol (carbamazepine), Dilantin (phenytoin), Depakote (valproic acid) and Zonegran (zonisamide).

One final area of interest would be to determine if there is a correlation between depression and the difference in MoCA scores between baseline and disease

progression. A correlation is a measure of how things are related, so understanding the strength and direction of this relationship, if one exists, would provide further awareness of the impact of depression on the reliability of the MoCA being used as an early identifier of disease progression. Depression would be quantified by utilizing scores from a routinely used depression screening tool known as the Patient Health Questionnaire-9 (PHQ-9; see Table 1 for the scoring interpretation and Appendix C for a complete example of the Spectrum Health modified version of the Pfizer Inc. questionnaire). The PHQ-9 score at disease progression would be used to assess depression. To test if there is a correlation between the depression screening tool scores and the difference in MoCA scores between baseline and disease progression, a Pearson correlation test would be used since both variables are continuous. The Pearson correlation test results in a value ranging anywhere from -1 to 1, where 0 represents no correlation. A value of -1 represents a perfect negative correlation or in terms specific to this study, it would confirm that as depression worsens, MoCA scores would become more abnormal. On the other end of the spectrum, a value of 1 represents a perfect positive correlation or in study-specific terms, a confirmation that as depression worsens, MoCA scores would become more normal. In effect, a very strong relationship in either direction would represent something similar to a confounder. It should not be necessary to utilize the nonparametric Spearman's rank correlation in this instance.

Table 1. Scoring interpretation of the PHQ-9 depression screening tool (20).

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

Sample Size Determination. A sample size of 34 subjects would be required to accomplish our specific aims with a standard power level of 0.8; however, to test the additional statistical models described above at a power of 0.8 required an increase in that number to 128 subjects. Our study goal would be to attain 128 subjects to maximize our power to the standard level. If the goal of 128 subjects was not achievable within the parameters and constraints surrounding the conduct of the study, the objective would be to maximize the sample size while being sure to surpass 34 subjects. Maximizing the sample size would consequentially elevate the power level to as near 0.8 as possible. Significance would be set at the standard level of 0.05.

Chapter 4 Results

Identifying Our Study Group

The statistical plan that drove the study design required a sample size of 128

subjects. Even with a list of 325 subjects with good potential, reaching this number

seemed a bit challenging, but by no means did we foresee a final enrollment of 5. This

was largely due to the fact that patients were not consistently receiving MoCAs at every

office visit, which was the assumed standard of care within the Spectrum Health Brain

and Spine Tumor Center for those individuals with a glioma. 254 of the 325 potential

subjects did not have 3 MoCAs, a requirement under the protocol's eligibility criteria.

This left only 71 potential subjects having at least 3 MoCAs that still needed to be

evaluated for secondary eligibility criteria. Of those 71 potential subjects, 30 were

excluded because they did not have a diagnostic pathology demonstrating a high grade

glioma. Of the final 41 potential subjects that had at least 3 MoCAs and a high grade

glioma pathology, 36 were excluded because their MoCAs did not align with the specific

time points described in the protocol. This also included subjects that did not

demonstrate a recurrence within the retrospective data collection window. With the

surprising difficulty of finding eligible subjects, we fortunately identified 5 subjects who

did meet all study criteria and were enrolled for study specific data collection. Table 2

details the screening breakdown.

5 enrolled subjects is quite a disparity from the 128 needed to power our

statistical tests, so the results being shared, although tested as intended, do not have

the statistical strength to validate the research questions we sought to answer. What it

does do, is help us recognize patterns that could positively change patient care within the Spectrum Health Brain and Spine Tumor Center and provide a foundation from which to build future research projects.

Table 2. Screening breakdown from 325 potential subjects to 5 enrolled subjects.

Screening group		325
1st exclusion - Did not have ≥ 3 MoCAs	-	254
2nd exclusion - No high grade diagnosis	-	30
3rd exclusion - MoCAs do not align with protocol	-	36
Remaining (study group)	=	5

Screening Group Descriptive Statistics

A more in depth look at the descriptive statistics acquired from our screening group exposes a more realistic look at the routine use of the MoCA within the Spectrum Health Brain and Spine Tumor Center. As mentioned before, we retrospectively screened 325 potential subjects (132 expired). Within this population, 500 total MoCAs were performed inside of the data collection window of September 1, 2013 to August 11, 2017. The number of MoCAs performed per individual ranged from 0 to 13 (Table 3). Understanding the number of MoCAs being performed at Spectrum Health under certain parameters was felt to be beneficial, so additional population data on tumor grade and pathology was captured for examination. In Tables 4 and 5, the distribution of potential subjects by tumor grade is displayed along with a representation of how the number of MoCAs (a minimum of 3) are dispersed in specifically the potential high grade subjects. In Table 6, the pathologies of the 325 potential subjects are listed, along with a count of those diagnosed and an average of the number of MoCAs conducted for that particular pathology.

Table 3. Numerical distribution of screened subjects by quantity of completed MoCAs.

Completed MoCAs	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of subjects	185	43	26	18	12	12	6	7	4	6	1	0	3	2

Table 4. Numerical distribution of screened subjects by WHO tumor grade.

WHO tumor grade	Number of subjects
1	21
2	42
3	59
4	150
N/A	53

Table 5. Numerical distribution of high grade screened subjects by quantity of completed MoCAs (≥ 3).

Completed MoCAs	3	4	5	6	7	8	9	10	11	12	13
Number of high grade subjects	11	6	6	2	5	3	5	1	0	1	1

Table 6. Numerical distribution of screened subjects by pathology, along with each group's average number of completed MoCAs.

Pathology	Number of subjects	Average number of completed MoCAs
Anaplastic astrocytoma	43	2.4
Anaplastic oligoastrocytoma	1	0
Anaplastic oligodendroglioma	14	1.6
Anaplastic pleomorphic xanthoastrocytoma	1	0
Astrocytoma	20	1.2
Dysembryoplastic neuroepithelial tumor	2	3
Ependymoma	5	0.2
Ganglioglioma	2	0
Glioblastoma	143	1.2
Gliomatosis cerebri	1	0
Gliosarcoma	6	1
Metastatic disease	16	3.5
N/A	37	0.8
Oligodendroglioma	18	3.4
Pilocytic astrocytoma	14	1.4
Subependymoma	2	1.5

Study Group Descriptive Statistics

The demographics of the study group included 4 males and 1 female, all identified as Caucasian. 4 of the 5 subjects were expired at the time of IRB approval. Glioblastoma accounted for the diagnosis of 4 of the subjects, while anaplastic astrocytoma accounted for just 1. The average age at the time of surgery was 55.8 ± 22.2 years. A gross total resection was performed on 3 subjects within the group, while subtotal resection was performed on the other 2. MRI was the imaging technique that identified tumor progression for all subjects. The average time from surgery to disease progression was approximately 1 year (354.2 ± 63.7 days). When grouped by resection type, subjects with gross total resection averaged 359.7 ± 86.2 days before disease progression, while subject with subtotal resection averaged 346.0 ± 33.9 days. As a

whole, the average time from the last radiation dose to disease progression was roughly

9 months (278.4 ± 67.9 days).

Results from Specific Aim 1

The study objectives included two specific aims. The first was to determine

whether there was a statistically significant decline in MoCA scores from a

predetermined baseline to disease progression. To test the difference in MoCA scores

between baseline and disease progression as described in specific aim 1, we used a

parametric paired t-test since the difference in MoCA scores was normally distributed.

The test for normality used in this instance was the Shapiro-Wilk test (w = 0.96, p =

0.81). The paired t-test, in essence, takes the average value of all patients' baseline

MoCA scores minus their disease progression MoCA scores and compares that to zero.

We determined whether that difference was significantly different from zero. The

average score of the baseline MoCA amongst the group was 25.4 ± 4.0, while the

average score of the disease progression MoCA was 26.0 ± 4.1. Our test concluded

that there was no statistically significant evidence to suggest a difference between the

baseline and disease progression MoCA scores (t=-1.18, p=0.30). Although not

significant, the negative test statistic indicates an upward trend or an improvement in

MoCA scores at disease progression.

Results from Specific Aim 2

The second specific aim was to determine the average time point between

baseline and disease progression where MoCA scores demonstrate the greatest

magnitude of change between consecutive assessments. This was calculated using

rudimentary calculations. Taking into account a few stipulations with regard to which

data points would be acceptable (described in the Primary Analysis of the Statistical

Plan), our data demonstrated a mean of 20.8 ± 29.0 days. In other words, on average,

our study group had the largest decline in MoCA scores occur 20.8 days before

identifying disease progression radiographically. Described with a little more detail, the

largest decline in MoCA scores in 3 of our subjects occurred at disease progression or

day 0. The other two subjects had their largest declining magnitude of change at 60 and

44 days prior to disease progression, respectively. A visual representation of each

subject's MoCA scores by way of a line graph is displayed in Figure 3.
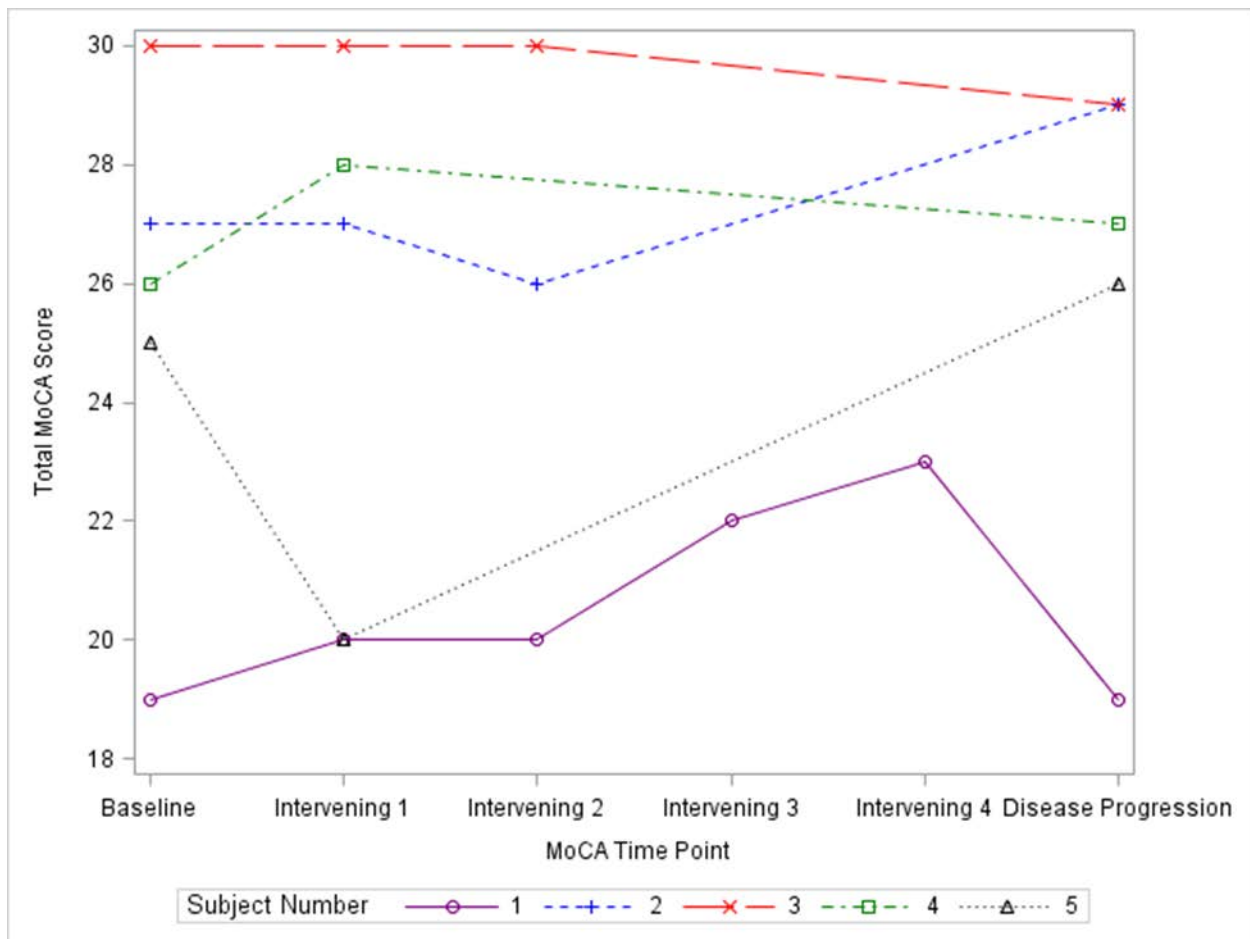
Figure 3. Line graph displaying the total score of each MoCA from baseline to disease progression by subject.

Results from Secondary Objectives

Our secondary analysis involved taking a hard look at a variety of demographic groupings in hopes to identify whether any of these were confounding variables that influenced the difference in MoCA scores between baseline and disease progression. Essentially, we were going to compare two groups to see whether there was a significant difference between them. If there was, then the variable would be considered a confounder. We planned to test this using a series of parametric two sample independent t-tests, however due to the size of our sample this was felt to be

impractical. Taking an already small group and breaking it down even further would

likely provide nonsensical results at best and at worst the tests would just be impossible

to run. Instead, we just captured descriptive statistics on our demographic groupings of

interest to at least provide some understanding of our subjects. The frequency and

percentage for each demographic grouping is displayed in Table 7.

Table 7. Frequency and percentage for each demographic grouping.

Age	
18-59	3 (60)
≥ 60	2 (40)
WHO tumor grade	
3	1 (20)
4	4 (80)
Chemotherapy at disease progression (On)	3 (60)
Stimulants at disease progression (On)	1 (20)
Antidepressants at disease progression (On)	1 (20)
Anti-epileptic drugs at disease progression (On)	4 (80)

The final demographic grouping of interest that we tested as a potential

confounding variable was depression. This variable was quantified using scores from a

depression screening tool (PHQ-9) rather than a simple yes or no to depression as we

had done for the other demographic groupings. We chose a Pearson correlation test for

this particular scenario. A correlation is a measure of how two events are related, so

essentially a very strong relationship in either direction would represent something

similar to a confounder. In our study design, we used the PHQ-9 score at disease

progression as our measure of depression. 3 of our 5 subjects had a PHQ-9 score of 0

at disease progression, which basically means they had no depression at that time. The

other 2 had scores of 4 and 9, which are examples of higher end minimal and mild

depression, respectively. The average or mean depression score for the sample at

disease progression was 2.6 ± 3.97. When our data was run through our correlation

test, we found a correlation coefficient of 0.63, which was not statistically significant due

to our small sample size of 5. This did, however, show a trend that if disease

progression MoCA scores are lower than baseline MoCA scores, then PHQ-9 is

decreasing. In other words, as cognitive decline is observed through MoCAs, subjects

also become less depressed.

Additional Statistics from the Study Group

Finally, here are a few additional items that were captured in our statistical

analysis to improve our overall understanding and to assist with the planning of any

future research. We calculated the average number of intervening MoCAs for all

subjects at 2 ± 1.2. Table 8 shows the numerical distribution by subject. We also broke

down all the MoCAs scores and took a look at how each subject fared by cognitive

domain. Since this was slightly complex due to a variation of maximum scores per

domain, we instead looked at the subject's percentage of perfect scores for each

domain. Table 9 provides a visual of this breakdown. Lastly, the tumor locations for all

subjects were captured to potentially breakdown domain scores by tumor location. The

distribution of tumors by location is represented in Table 10.

Table 8. Number of intervening MoCAs by subject.

Subject number	Number of intervening MoCAs
1	4
2	2
3	2
4	1
5	1

Table 9. Percentage of perfect scores within each MoCA cognitive domain by subject.

Domain	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
Visuospatial executive	0%	75%	100%	100%	67%
Naming	83%	75%	100%	100%	100%
Attention (list of digits)	83%	75%	100%	100%	67%
Attention (list of letters)	100%	100%	100%	100%	100%
Attention (serial 7 subtraction)	67%	100%	100%	33%	67%
Language (repeat)	83%	100%	100%	100%	67%
Language (fluency)	0%	100%	100%	100%	33%
Abstraction	0%	50%	75%	67%	67%
Delayed recall	0%	0%	75%	33%	0%
Orientation	33%	75%	75%	67%	67%

Table 10. Tumor location by subject.

Subject number	Left frontal	Right frontal	Left temporal	Right temporal	Left parietal	Right parietal
1	x		x			
2						x
3					x	
4	x					
5		x		x		

Chapter 5 Discussion and Conclusions

Study Recap

The goal of our study was to evaluate whether the MoCA could be adopted as a reliable, early identifier of high grade glioma progression. If this were proven true, in addition to the MoCA undoubtedly providing patients earlier options for medical intervention, it could also have the capacity to be used as an alternative to MRI or CT surveillance and limit the burden of radiographic imaging in the high grade glioma population. This novel concept began as a simple desire to examine the MoCA in conjunction with routine surveillance MRIs, however, after a thorough literature review, it evolved into its current state. The most influential piece of literature uncovered in that review was a study by Meyers and Hess examining cognitive deterioration in patients with recurrent brain tumors. Using a battery of standardized psychometric tests, their work suggested a pattern of measurable brain function decline approximately 6 weeks prior to radiographic evidence of tumor progression (4). In essence, Meyers and Hess laid the foundation for our research design. We built a comparable study focusing on high grade glioma patients and hoped to display similar results using the MoCA as our standardized psychometric test.

Study Complications

All research is bound to have complications, even with a well thought out plan, and we were no different. Our study design took months to develop, and looking back, it is hard to see where we could have done anything differently. We moved forward with the information we had and conducted the study to the best of our ability. Unfortunately,

we ran into a pretty serious issue with regard to enrollment. Our statistical plan required

a sample size of 34 subjects to test our primary objectives and 128 subjects for our

secondary objectives. We had concerns from the beginning that 128 subjects might be

difficult to obtain due to a preliminary search report that estimated that we would have

access to only 271 subjects with a moderately high potential of meeting our eligibility

criteria. Because of our concerns we aimed for the enrollment of 128 subjects, but left

ourselves an escape clause within the protocol in the event our enrollment goal was not

achievable. Our means of escape was to enroll as many subjects as feasibly possible

beyond 34. Our hope was to test our primary objectives as intended and elevate the

statistical power of our secondary objectives to as high of a level as possible. When all

was said and done, our final enrollment was 5, a considerable difference from anything

we could have imagined, even with initial concerns.

In an effort to examine this discrepancy in more detail we reviewed some of the

data collected during the screening process. We wanted to better understand why only

5 subjects met the study criteria of 325 solid potentials. The first step in the screening

process was to identify the subjects with a minimum of 3 MoCAs, a study requirement. It

was discovered that only 71 of 325 subjects met this requirement. This was an

extremely shocking result because it was understood from conversations during the

planning of the study that it was standard practice within the Spectrum Health Brain and

Spine Tumor Center for all subjects with a brain tumor to have a MoCA performed along

with every scheduled MRI. This was an expectation that the study design relied on to be

conducted as intended and unfortunately the authenticity of that expectation could not

be verified at that time without an IRB approval to review patient records. Clearly, had we known that we would only have access to 71 potential subjects, alterations to the protocol would have been made at a very early stage. In addition to this damaging discovery, we also had to eliminate 30 subjects from the group of 71 for not having a high grade glioma diagnosis and 36 because their MoCAs did not align with protocol expectations. These last two items were not unexpected and probably wouldn't have been as impressive had the original sample been receiving MoCAs as we had anticipated. Another surprising fact was that subjects diagnosed with a glioblastoma (the largest subgroup - 143 subjects) only averaged 1.2 completed MoCAs. This subgroup has the most severe diagnosis and in theory would seem to be the group that would benefit the most from completing serial MoCAs.

At the current time, we have no solid explanation for the paucity of MoCAs performed within the Spectrum Health Brain and Spine Tumor Center. I'm sure there are many factors that have contributed to this result, such as patient expiration, patient refusal, time constraints and untrained/unfamiliar clinic staffing, but instead of looking at this as a mishap or oversight, I see this as an opportunity. We can utilize the results that we uncovered during our screening process and share this with the neurologists who practice at this location. If their intention is to truly conduct MoCAs on this population as frequently as it was conveyed, then this information has uncovered a deficiency and provides a solid and validated foundation for future process improvements.

Anticipated Versus Actual Results

The final enrollment total of 5 is quite a distance from our intended sample size. 128 enrolled subjects would have guaranteed us enough statistical power to validate our results as accurate. During our analysis, and when able, we tested our 5 subjects as intended, to learn as much as possible even though the data is not statistically significant. Below is our reflection on our anticipated versus actual results for our specific aims and secondary objectives.

Based on inference from past studies and prior anecdotal evidence, we anticipated that specific aim 1 would show a statistically significant decline in MoCA scores from baseline to disease progression. We tested our 5 subjects using a parametric paired t-test and it concluded that there was no statistically significant evidence to suggest a difference between the baseline and disease progression MoCA scores (t=-1.18, p=0.30). The negative test statistic indicates an upward trend in MoCA scores at disease progression, which is the opposite of what we had predicted. We clearly don't have enough subjects to trust this result, but if we had this information from the proper sample size (34 subjects), it would have been a clear stopping point in our analysis because additional aims and objectives would not have significance if there were no decline in cognitive function.

In specific aim 2, we predicted that the average time point between baseline and disease progression where MoCA scores might show the greatest magnitude of change between consecutive assessments would be approximately 60 days prior to disease

progression. 60 days was chosen as the anticipated outcome due to the limitations in frequency of routinely administered MoCAs in the setting of this research. The Spectrum Health Brain and Spine Tumor Center only performs MoCAs at the time of radiographic imaging, thus the shortest duration between sequential imaging/MoCAs for routine observation of a high grade glioma is roughly 60 days. This would be the MoCA closest in proximity to the 6 week mark, which was proven to be the time point where disease progression could be identified from psychometric tests in the Meyers and Hess study (4). The results from our 5 subjects were calculated using rudimentary calculations as we had always intended and because of this we did not require any particular sample size. Our data demonstrated a mean of 20.8 ± 29.0 days. In other words, our study group on average had their largest decline in MoCA scores occur 20.8 days before identifying disease progression radiographically. Although it was exciting to see a decline in MoCA scores in advance of disease progression, a standard deviation of ± 29.0 days really shows how widespread the data points were and does not bring with it a lot of confidence in this result. Nevertheless, there is still some hope that with a solid sample size and a significant decline in specific aim 1, seeing the largest decline in MoCA scores weeks in advance of disease progression could provide some treatment options for this population.

With regard to the testing of our chosen demographic groupings, we did feel there was potential for us to uncover a confounding variable that would influence the difference in MoCA scores between baseline and disease progression. We had planned to use a series of parametric two sample independent t-tests, but the sample size of 5

was too small to break the group down even further. An intended sample size of 128 would have not only allowed us to test for confounders, but in addition it would have given us the statistical strength to validate the results. Nevertheless, we were still able to provide descriptive statistics on these demographic groups. The frequency and percentage for each group is broken down in Table 6. If any of these demographic groupings had been tested as intended and identified as a confounder, the bulleted list below describes what we anticipated their influence would be on MoCA scores in either positive or negative directions and our justification for that prediction.

- Age: Individuals who are advanced in age are at an increased risk for cognitive impairment and decline, therefore they may be more susceptible to cognitive decline associated with tumor progression and exhibit diminished MoCA scores.

- Tumor Grade: Grade IV tumors are more aggressive and infiltrative than lower grades and as a result may be associated with considerable cognitive decline and inferior MoCA scores.

- Chemotherapy: Treatment such as chemotherapy can cause fatigue and attentional deficits, which could negatively affect MoCA scores.

- Stimulants: The ability of these types of medications to increase focus may enhance performance on MoCA testing.

- Antidepressants: The ability of these medications to alleviate symptoms of depression and anxiety may improve MoCA scores (although the presence of depression may lead to lower scores).

- Anti-Epileptic Drugs: Medication may cause cognitive slowing and lower MoCA scores.

Lastly, our final demographic grouping of interest that we wanted to test as a potential confounding variable was depression. Because depression was quantified using PHQ-9 scores rather than a simple yes or no to depression as we had done for the other demographic groupings, we had to use a Pearson correlation test. Our goal was to determine if there was a correlation or a very strong relationship between depression and the difference in MoCA scores between baseline and disease progression. We anticipated a negatively correlated relationship due to commonly known effects of depression such as low mood, anxiety and fatigue adversely influencing MoCA scores. Our actual result, although not statistically significant, was a correlation coefficient of 0.63. This demonstrated a positively correlated relationship, the opposite of what we had anticipated. In other words, the positive correlation coefficient suggests that the known effects of depression would actually favorably influence MoCA scores. Our outcome is a bit peculiar and we don't have any justification for it other than a small sample size; However, identifying factors in this situation that would produce a positive correlation would make for an intriguing study.

Additional Observations

We anticipated that we would see certain trends when examining the MoCA scores. One was an overall decline in MoCA scores from baseline to disease progression. Only 1 of our 5 subjects followed this course and the decline in MoCA score was a meager 1 point, so from a macro view, this seems insignificant. A second trend we expected to observe was that the greatest magnitude of change in MoCA scores (decline only) would occur somewhere in between baseline and disease

progression, providing us some advance notice of possible progression. This occurred

with 2 of our 5 subjects, while the other 3 demonstrated their greatest magnitude of

change at disease progression. Because this trend was a bit more balanced, we felt as

though examining these two groups for similarities and differences may be beneficial.

The two that demonstrated our anticipated trend were subjects #2 and #5. We

will call this the anticipated group. The 3 who did not demonstrate what we had

anticipated consisted of subjects #1, #3 and #4. We will identify this group as the

unanticipated group. The anticipated group was much older at disease progression than

the unanticipated group with average ages of 78 and 42.3, respectively. The tumor

locations for both groups were in the frontal, temporal and parietal lobes, but what was

interesting was that the tumor locations for the anticipated group were only on the right

portion of the lobes and those for the unanticipated group were only on the left portion

of lobes. We thought there might be a pattern with regard to tumor location and the

MoCA subscores by cognitive domain, but this was not the case. We did, however,

observe some visual patterns while investigating cognitive domain subscores (Table 9),

but these were not fixed to our anticipated or unanticipated groups. All 5 subjects clearly

demonstrated difficulty with the delayed recall domain, while attention (list of letters)

was undoubtedly the most successful, as evidenced by perfect scores from all. One

additional item of note was that subjects #3 and #4 demonstrated very similar cognitive

domain subscores, but this doesn't factor well with our cross-examination by group

because subject #1, the third piece to our unanticipated group, is clearly different. In

addition, we see no real similarities between subjects #2 and #5, our anticipated group.

One last area to acknowledge was the breakdown of some of the other groups of interest. The anticipated group showed no similarities except for age. The unanticipated group, however was pretty consistent. At the time of disease progression, all 3 subjects were on anti-epileptic drugs, off antidepressants, off stimulants and 2 of 3 were on some form of chemotherapy. Although, this study delved no further into these patterns, it might be useful to re-examine these relationships in future studies with a larger sample.

Study Limitations

The success of any research project depends a great deal on its design. Even though this sounds simple, it is actually quite complex because multiple factors influence a study's design, such as the research question, objectives, population, funding and time. Our study design was carefully thought out, but factors existed that led to some limitations that repressed the power of the study.

Both time constraints for the study and the short-term survival of this patient population led us to the decision to conduct a retrospective design, which brought about its own limitations. First, preliminary research preparation was limited because we could not examine what was in the EMR without IRB approval. Second, conducting a retrospective trial meant that we were at the mercy of what had been documented in the EMR by clinicians. In essence, there was no control over the conduct of MoCAs, specifically when they were performed and how consistently this was done amongst the population. In addition, we had no oversight of the data documentation within the EMR. This means that even if the data we were trying to obtain was stored in the EMR, it was

sometimes difficult, if not impossible to find due to individual variations in the naming and storage location of the data.

There are other study limitations that existed as well, but didn't play as crucial a part as those discussed above. In truth, we knew very well that a retrospective trial with time constraints would have some hurdles, but despite the circumstances, we are still very pleased with our study design. In fact, we believe a future variation would only require very slight modifications to properly test many of our objectives.

Future Direction

Our study design is very solid and with a couple tweaks, future projects could easily see success. My first of two recommendations for building on our solid foundation would be to convert our protocol into a prospective study. This would require patient consent instead of the waiver of consent and HIPAA authorization we were given, but it would allow for greater control over the consistent use of the MoCA within the clinic setting, stipulating in the protocol that the MoCAs be properly completed and performed at time points aligning with MRI surveillance. My second recommendation would be to remove the secondary objectives where we were attempting to identify confounding variables. These are very important questions to address and would really strengthen the validity of the MoCA being used as an early identifier of disease progression, but most of these objectives required our sample size to be increased from 34 to 128 and this could be prohibitive in terms of budget and subject availability. A prospective enrollment of 34 would be much more feasible, especially for an uncommon diagnosis,

and enrolling 34 subjects would still be a sufficient sample size to properly test the specific aims. If the results were promising, extending out enrollment to 128 may seem more reasonable with regard to time and resources.

Conclusion

MRI is clearly the medical community's primary tool for identifying disease progression in the high grade glioma population. Finding a reliable substitute that is cost effective and perhaps provides advance warning is of great interest to physicians in this field and patients of this population, yet little research has been done to identify an alternative. Building from ideas in previous research, we designed a study to assess whether or not the MoCA, a cognitive assessment tool, could be identified as a reliable early identifier of disease progression in this population.

Our results were not able to support the MoCA as a reliable and early identifier of disease progression as we had hypothesized, mainly due to our small sample. Our difficulty enrolling our intended sample size greatly impacted our statistical tests, leaving the majority of our results insignificant. What we learned from our sample was that MoCA scores actually improved from baseline to disease progression. A recent study examining neurocognitive function in patients with glioblastoma demonstrated evidence of neurocognitive decline at the time of progression in patients with investigator-determined progressive disease (21). Our outcome is considerably different from what similar research has shown. We also identified that our study group on average had their largest decline in MoCA scores 20.8 days before identifying disease progression

radiographically. This is definitely an encouraging result because there is potential for identifying progression in advance of an MRI. Lastly, we identified a positive correlation between depression and the difference in MoCA scores between baseline and disease progression, which suggests that the known effects of depression favorably influence MoCA scores. This is quite the contrary to most research on depression and cognitive function. A 2011 article analyzing observational studies that examined depression in patients with glioma found that depression was consistently associated with cognitive dysfunction (22).

Even with enrollment difficulty and some unexpected outcomes, our research contributed a solid study design and identified some interesting areas for exploration. We definitely feel the MoCA has potential to address our hypothesis. Hopefully, this study will provide a basis for a more thorough investigation of the MoCA and its use as an early and reliable identifier of disease progression in the high grade glioma population.

Appendix A

- Montreal Cognitive Assessment version 7.1 (original version).
- Montreal Cognitive Assessment version 7.2 (alternate version).
- Montreal Cognitive Assessment version 7.3 (alternate version) (12).

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education :   Date of birth :
Sex :   DATE :

VISUOSPATIAL / EXECUTIVE		POINTS

Copy cube

Draw CLOCK (Ten past eleven)
(3 points)

[ ]   [ ]   [ ]   [ ]   [ ]   __/5
                         Contour   Numbers   Hands

NAMING

[ ]   [ ]   [ ]   __/3

MEMORY	Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.		FACE	VELVET	CHURCH	DAISY	RED	No points
		1st trial						
		2nd trial						

ATTENTION	Read list of digits (1 digit/ sec.).	Subject has to repeat them in the forward order	[ ] 2 1 8 5 4	__/2
		Subject has to repeat them in the backward order	[ ] 7 4 2	

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ]   F B A C M N A A J K L B A F A K D E A A A J A M O F A A B   __/1

Serial 7 subtraction starting at 100   [ ] 93   [ ] 86   [ ] 79   [ ] 72   [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**   __/3

LANGUAGE	Repeat : I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ]	__/2
	Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)	__/1

ABSTRACTION	Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler	__/2

DELAYED RECALL	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only	__/5
Optional	Category cue							
	Multiple choice cue							

ORIENTATION	[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City	__/6

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TOTAL   __/30
Add 1 point if   ≤ 12 yr edu

Administered by: _____

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MONTREAL COGNITIVE ASSESSMENT (MOCA®)
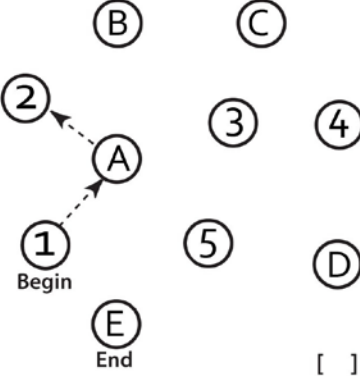## Version 7.2 Alternative Version
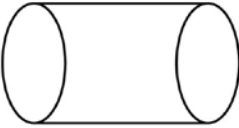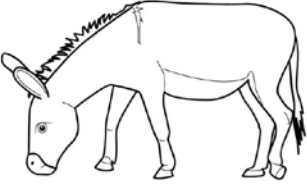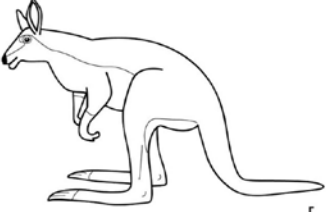
NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE		POINTS

Copy rectangle

Draw CLOCK (Five past four)
(3 points)

Ⓒ Ⓓ
③
④ ⑤
Ⓑ
② ①
Begin
Ⓐ
Ⓔ
End

[ ]   [ ]

[ ]   [ ]   [ ]
Contour   Numbers   Hands

___/5

NAMING

[ ]   [ ]   [ ]   ___/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

		TRUCK	BANANA	VIOLIN	DESK	GREEN	No points
	1st trial						
	2nd trial						

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order	[ ] 3 2 9 6 5	
Subject has to repeat them in the backward order	[ ] 8 5 2	___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ]   F B A C M N A A J K L B A F A K D E A A A J A M O F A A B   ___/1

Serial 7 subtraction starting at 90   [ ] 83   [ ] 76   [ ] 69   [ ] 62   [ ] 55

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**   ___/3

LANGUAGE

Repeat : A bird can fly into closed windows when it's dark and windy. [ ]	
The caring grandmother sent groceries over a week ago. [ ]	___/2

Fluency / Name maximum number of words in one minute that begin with the letter S   [ ] _____ (N ≥ 11 words)   ___/1

ABSTRACTION — Similarity between e.g. carrot - potato = vegetable. [ ] diamond - ruby [ ] cannon - rifle   ___/2

DELAYED RECALL

		TRUCK	BANANA	VIOLIN	DESK	GREEN		
	Has to recall words **WITH NO CUE**	[ ]	[ ]	[ ]	[ ]	[ ]	Points for UNCUED recall only	___/5
Optional	Category cue							
	Multiple choice cue							

ORIENTATION   [ ] Date   [ ] Month   [ ] Year   [ ] Day   [ ] Place   [ ] City   ___/6

Adapted by : Z. Nasreddine MD, N. Phillips PhD, H. Chertkow MD
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Administered by: _____

Normal ≥ 26 / 30

TOTAL   ___/30
Add 1 point if ≤ 12 yr edu

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.3 Alternative Version

NAME :
Education :   Date of birth :
Sex :   DATE :

VISUOSPATIAL / EXECUTIVE		POINTS

Copy cylinder

Draw CLOCK (Ten past nine)
(3 points)

B   C

2

A

3   4

1

5

Begin

D

E
End

[ ]

[ ]

[ ]   [ ]   [ ]
Contour   Numbers   Hands

___/5

NAMING

[ ]   [ ]   [ ]   ___/3

MEMORY	Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.		TRAIN	EGG	HAT	CHAIR	BLUE	No points
		1st trial						
		2nd trial						

ATTENTION	Read list of digits (1 digit/ sec.).	Subject has to repeat them in the forward order	[ ] 5 4 1 8 7	
		Subject has to repeat them in the backward order	[ ] 1 7 4	___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ]   F B A C M N A A J K L B A F A K D E A A A J A M O F A A B   ___/1

Serial 7 subtraction starting at 80   [ ] 73   [ ] 66   [ ] 59   [ ] 52   [ ] 45   ___/3
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

LANGUAGE	Repeat : She heard his lawyer was the one to sue after the accident. [ ] The little girls who were given too much candy got stomach aches. [ ]	___/2

Fluency / Name maximum number of words in one minute that begin with the letter B   [ ] _____ (N ≥ 11 words)   ___/1

ABSTRACTION	Similarity between e.g. banana - orange = fruit [ ] eye – ear [ ] trumpet – piano	___/2

DELAYED RECALL	Has to recall words **WITH NO CUE**	TRAIN [ ]	EGG [ ]	HAT [ ]	CHAIR [ ]	BLUE [ ]	Points for UNCUED recall only	___/5
Optional	Category cue							
	Multiple choice cue							

ORIENTATION	[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City	___/6

Adapted by : Z. Nasreddine MD, N. Phillips PhD, H. Chertkow MD
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Administered by: _____

Normal ≥ 26 / 30

TOTAL   ___/30
Add 1 point if   ≤ 12 yr edu

Appendix B

- REDCap data collection tool dated 08/30/2017 (23).

Demographics

Study ID Number

_____

Date of Birth

_____

Gender

○ Male
○ Female

Race

○ American Indian or Alaska Native
○ Asian
○ Black or African Heritage
○ Native Hawaiian or Pacific Islander
○ White or Caucasian
○ Hispanic or Latino
○ Unknown

REDCap

Medical Data

Tumor Type

_____

WHO grade
- ◯ Grade 3
- ◯ Grade 4
- ◯ Undetermined, but High Grade

Tumor Location
At Time of Diagnosis (First Imaging)
- ☐ Brain Stem
- ☐ Cerebellum
- ☐ Left Frontal
- ☐ Right Frontal
- ☐ Left Temporal
- ☐ Right Temporal
- ☐ Left Parietal
- ☐ Right Parietal
- ☐ Left Occipital
- ☐ Right Occipital
- ☐ Other, Please Specify
- ☐ Unknown

Other Location

_____

Surgery (or Biopsy) Start Date

_____

Surgery Type
- ◯ Gross Total Resection
- ◯ Subtotal Resection
- ◯ Biopsy
- ◯ Unknown

Disease Progression Date (Date of Initial Diagnostic Imaging)

_____

Radiographic Imaging Used to Identify Disease Progression
- ☐ MRI
- ☐ CT Scan
- ☐ Other, Please Specify
- ☐ Unknown

Other Imaging

_____

Age at Disease Progression

_____

Date of the Last Radiation Dose From the Treatment Regimen Following Resection/Biopsy

_____

Time (Days) Between Last Radiation Dose and Disease Progression

_____

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REDCap

Groupings of Interest

Chemotherapy at Disease Progression
- ○ On
- ○ Off
- ○ Unknown

Stimulants at Disease Progression
- ○ On
- ○ Off
- ○ Unknown

Antidepressants at Disease Progression
- ○ On
- ○ Off
- ○ Unknown

Anti-Epileptic Drugs at Disease Progression
- ○ On
- ○ Off
- ○ Unknown

Depression at Disease Progression (PHQ-9 Score)
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6
- ○ 7
- ○ 8
- ○ 9
- ○ 10
- ○ 11
- ○ 12
- ○ 13
- ○ 14
- ○ 15
- ○ 16
- ○ 17
- ○ 18
- ○ 19
- ○ 20
- ○ 21
- ○ 22
- ○ 23
- ○ 24
- ○ 25
- ○ 26
- ○ 27
- ○ Unknown

Baseline MoCA

Date of Baseline MoCA _____

Visuospatial/Executive
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5

Naming
- ○ 0
- ○ 1
- ○ 2
- ○ 3

Attention (List of Digits)
- ○ 0
- ○ 1
- ○ 2

Attention (List of Letters)
- ○ 0
- ○ 1

Attention (Serial 7 Subtraction)
- ○ 0
- ○ 1
- ○ 2
- ○ 3

Language (Repeat)
- ○ 0
- ○ 1
- ○ 2

Language (Fluency)
- ○ 0
- ○ 1

Abstraction
- ○ 0
- ○ 1
- ○ 2

Delayed Recall
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5

Orientation
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6

REDCap

Total Score

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6
- ○ 7
- ○ 8
- ○ 9
- ○ 10
- ○ 11
- ○ 12
- ○ 13
- ○ 14
- ○ 15
- ○ 16
- ○ 17
- ○ 18
- ○ 19
- ○ 20
- ○ 21
- ○ 22
- ○ 23
- ○ 24
- ○ 25
- ○ 26
- ○ 27
- ○ 28
- ○ 29
- ○ 30

Intervening MoCA(s)

Date of Intervening MoCA   _____

Visuospatial/Executive
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5

Naming
- ○ 0
- ○ 1
- ○ 2
- ○ 3

Attention (List of Digits)
- ○ 0
- ○ 1
- ○ 2

Attention (List of Letters)
- ○ 0
- ○ 1

Attention (Serial 7 Subtraction)
- ○ 0
- ○ 1
- ○ 2
- ○ 3

Language (Repeat)
- ○ 0
- ○ 1
- ○ 2

Language (Fluency)
- ○ 0
- ○ 1

Abstraction
- ○ 0
- ○ 1
- ○ 2

Delayed Recall
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5

Orientation
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6

Total Score

○ 0
○ 1
○ 2
○ 3
○ 4
○ 5
○ 6
○ 7
○ 8
○ 9
○ 10
○ 11
○ 12
○ 13
○ 14
○ 15
○ 16
○ 17
○ 18
○ 19
○ 20
○ 21
○ 22
○ 23
○ 24
○ 25
○ 26
○ 27
○ 28
○ 29
○ 30

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REDCap

Disease Progression MoCA

Date of Disease Progression MoCA   _____

Visuospatial/Executive
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5

Naming
- ○ 0
- ○ 1
- ○ 2
- ○ 3

Attention (List of Digits)
- ○ 0
- ○ 1
- ○ 2

Attention (List of Letters)
- ○ 0
- ○ 1

Attention (Serial 7 Subtraction)
- ○ 0
- ○ 1
- ○ 2
- ○ 3

Language (Repeat)
- ○ 0
- ○ 1
- ○ 2

Language (Fluency)
- ○ 0
- ○ 1

Abstraction
- ○ 0
- ○ 1
- ○ 2

Delayed Recall
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5

Orientation
- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6

REDCap

Total Score

○ 0
○ 1
○ 2
○ 3
○ 4
○ 5
○ 6
○ 7
○ 8
○ 9
○ 10
○ 11
○ 12
○ 13
○ 14
○ 15
○ 16
○ 17
○ 18
○ 19
○ 20
○ 21
○ 22
○ 23
○ 24
○ 25
○ 26
○ 27
○ 28
○ 29
○ 30

Expiration

Has Subject Expired On or Before the Study IRB
Approval Date?
○ Yes
○ No
○ Unknown

Expiration Date Status
○ The Full Date is Known
○ Only a Partial Date is Known
○ Unknown Date

Date of Expiration _____

Month of Expiration
○ Unknown
○ 1
○ 2
○ 3
○ 4
○ 5
○ 6
○ 7
○ 8
○ 9
○ 10
○ 11
○ 12

Day of Expiration
○ Unknown
○ 1
○ 2
○ 3
○ 4
○ 5
○ 6
○ 7
○ 8
○ 9
○ 10
○ 11
○ 12
○ 13
○ 14
○ 15
○ 16
○ 17
○ 18
○ 19
○ 20
○ 21
○ 22
○ 23
○ 24
○ 25
○ 26
○ 27
○ 28
○ 29
○ 30
○ 31

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Year of Expiration

- ⚪ Unknown
- ⚪ 2012
- ⚪ 2013
- ⚪ 2014
- ⚪ 2015
- ⚪ 2016
- ⚪ 2017
- ⚪ 2018
- ⚪ 2019
- ⚪ 2020

Appendix C

- Spectrum Health modified version of Pfizer Inc.'s Patient Health Questionnaire-9. Unaltered versions are publically available online (20).

Patient Name

DOB

MRN

Physician

FIN

Questionnaire/Downtime
PATIENT HEALTH QUESTIONNAIRE (PHQ-9)/
INSTRUCTIONS - GENERAL

DEPRESSION QUESTIONNAIRE Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all (0)	Several days (1)	More than half the days (2)	Nearly every day (3)
1. Having little interest or pleasure in doing things.	☐	☐	☐	☐
2. Feeling down, depressed or hopeless.	☐	☐	☐	☐
3. Trouble falling or staying asleep or sleeping too much.	☐	☐	☐	☐
4. Feeling tired or having little energy.	☐	☐	☐	☐
5. Having a poor appetite or overeating.	☐	☐	☐	☐
6. Feeling bad about yourself. Feeling that you are a failure or have let yourself or your family down.	☐	☐	☐	☐
7. Trouble concentrating on things, such as reading the newspaper or watching television.	☐	☐	☐	☐
8. One or the other: Moving or speaking so slowly that other people could have noticed. Or, being so fidgety or restless that you have been moving around a lot more than usual.	☐	☐	☐	☐
9. Thoughts that you would be better off dead or of hurting yourself in some way.	☐	☐	☐	☐

For staff use only:

Scoring   <u>0</u> +   _____ +   _____ +   _____

Total score   = _____

If you checked any boxes in the last 3 columns:

10. **How difficult have these problems made it for you to do your work, take care of things at home or get along with other people?**

   ☐ Not difficult at all   ☐ Somewhat difficult   ☐ Very difficult   ☐ Extremely difficult

I confirm this information is accurate.

DATE _____ Person Completing Form signature _____

If not patient/subject, then note relationship to patient/subject _____

DO NOT MARK BELOW THIS LINE   BARCODE ZONE   DO NOT MARK BELOW THIS LINE

* X 1 3 1 1 2 *

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)/INSTRUCTIONS - GENERAL *(CONTINUED)*

FOR STAFF TO USE.

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 ✓s in the shaded section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Consider Major Depressive Disorder

- if there are at least 5 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder

- if there are 2-4 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient.
Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓: Several days = 1 More than half the days = 2 Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying **PHQ-9 Scoring Box** to interpret the TOTAL score.
5. Results may be included in patient files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

Scoring: add up all checked boxes on PHQ-9

For every ✓ Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

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A2662B 10-04-2005

Appendix D

- Protocol version date July 27, 2017.

Use of the Montreal Cognitive Assessment as an Early Indicator of Tumor Progression in Patients with Stage III and IV Gliomas

Short Title: MoCA Study

Author:	Eric Laney, B.S.
Program:	Spectrum Health Office of Research Administration
	Research Operations
Institution:	Spectrum Health
Corresponding Author:	Eric Laney, B.S. Clinical Research Specialist 2 Spectrum Health Cancer Research 145 Michigan St. NE, Suite 6274, MC 317 Grand Rapids, MI 49503 Telephone: (616) 486-2074, Fax: (616) 486-6300 eric.laney@spectrumhealth.org

Version Date
July 27, 2017

Page 1 of 15

Table of Contents

1. **Protocol Title:** Use of the Montreal Cognitive Assessment as an Early Indicator of Tumor Progression in Patients with Stage III and IV Gliomas

2. **Investigator(s):** Wendy Sherman, MD (Primary), Steven Pastyrnak, Ph.D. (Sub) and Eric Laney, B.S. (Sub/Coordinator)

3. **Version Date:** July 27, 2017

4. **Objectives:** The purpose of this study is to evaluate whether the Montreal Cognitive Assessment (MoCA) could be adopted as a reliable, early identifier of disease progression in the high grade glioma population and thereby limit the burden of radiographic imaging.

   Specific Aim 1: Determine whether there is a statistically significant decline in MoCA scores from a predetermined baseline to disease progression.

   Specific Aim 2: Determine the average time point between baseline and disease progression where MoCA scores see the largest magnitude of change between consecutive assessments.

5. **Background:** The Montreal Cognitive Assessment or MoCA is a comprehensive cognitive screening test developed by Dr. Ziad Nasreddine, a neurologist who graduated from the University of Sherbrooke (Quebec) and completed his fellowship at the University of California, Los Angeles. Dr. Nasreddine's goal was to develop a quick, easy and comprehensive cognitive screening that is precise, sensitive and specific for use by clinicians of high volume, first line specialty clinics (1).

   The MoCA was first validated in 2000 when it showed excellent performance in distinguishing between cognitively intact and impaired groups classified by a gold standard neuropsychological assessment (1). Another validation study occurred between 2003 and 2004, which confirmed the test's ability to distinguish normal controls from subjects with mild cognitive impairment or mild Alzheimer's disease (2). More recently, in 2010, a scoring system was created for the memory cueing section of the MoCA, which had only been assessed qualitatively prior (1). This new system is called the Memory Index Score (MoCA-MIS) and it helps determine which subjects with mild cognitive impairment are most likely to transition to dementia over a follow-up period averaging 18 months. Results of a 2013 study showed that mild cognitively impaired subjects with low MoCA and MoCA-MIS scores were more likely to show a rapid progression to Alzheimer's disease (3). With studies validating the impact of MIS, it was eventually added to the MoCA as Version 8.1 (1).

   Although Version 8.1 of the MoCA has been created, Version 7.1 is still widely used (see Appendix A for an example of MoCA Version 7.1). The MoCA has been translated and adapted for 46 different languages and dialects and is used in 100 different countries. It is even offered in alternative versions to minimize any learning effects from multiple assessments within a timeframe of 3 months or less (1).

   The MoCA assesses the following domains: memory, language, conceptual thinking, attention and concentration, visuoconstructional skills, executive functions, orientation and calculations. The time to administer the MoCA is roughly 10 minutes and is scored on a scale from 0 to 30 points. Scores of 26 and above are considered normal (4). Although research standards have not been established for severity levels, the frequently asked

questions page of the official MoCA website discusses scores of 18-26 as being considered mild cognitive impairment, 10-17 as moderate and anything less than 10 as severe (5).

Because cognitive dysfunction has been associated with many neurological and systemic diseases, the MoCA has been found to be beneficial in detecting mild cognitive impairment in a diverse array of conditions such as Alzheimer's disease, Huntington's disease, Parkinson's disease, fronto-temporal dementia, amyotrophic lateral sclerosis (ALS), brain tumors and many others (1). One particular area of interest where the MoCA could be a useful tool is with brain tumors known as gliomas. Gliomas represent 25% of all primary brain tumors (originating in the brain) and 75% of all malignant tumors (6).

The word glioma is a general term that refers to all tumors arising from glial cells, a supportive tissue of the brain. Gliomas are classified by location, cell type and grade. Location is categorized by supratentorium, infratentorium, brainstem and spinal cord. The dividing boundary within the brain is a membrane known as the tentorium. Above this membrane is the cerebrum and below is the cerebellum and brainstem. Approximately 70% of adult tumors originate in the cerebrum and 70% of child tumors originate in the cerebellum (7). A much less common location, the brainstem, accounts for only 1-2% of adult gliomas (8). In contrast, the brainstem accounts for a much more prevalent 10-20% in the childhood population (9).

Gliomas are also classified by cell type. Within this classification system, the three main types are astrocytoma, oligodendroglioma and ependymoma. These names stem from the three varieties of glial cells that can form tumors, which are astrocytes, oligodendrocytes and ependymal cells. Some tumors actually display a mixture of these cell types and are known as mixed gliomas or oligoastrocytomas. Three other variations usually included in this classification system, but not necessarily confined to one particular cell type are brainstem gliomas, optic gliomas and gliomatosis cerebri (10). Brainstem glioma cell types are not typically specified because of limitations obtaining tissue due to location, optic gliomas are thought to be astrocytomas and gliomatosis cerebri is thought to be an astrocytic process.

The World Health Organization (WHO) also classifies gliomas and other brain tumors by grade. The tumor grades range from I to IV, where the higher the grade the more advanced the disease. Grade I tumors are typically non-cancerous, slow growing and are associated with long-term survival. Grade II tumors are relatively slow growing, show cellular atypia, may spread to normal tissue and can recur as a higher grade. Grade III tumors are malignant, are actively reproducing abnormal cells, are spreading into normal tissue and often recur as grade IV. Grade IV tumors are malignant, fast growing, actively reproducing abnormal cells, easily spread to normal tissue, often form new blood vessels to maintain their rapid growth and have areas of dead cells in their center known as necrosis due to their growth outpacing their blood supply (11).

High grade gliomas, grades III and IV, are the most aggressive gliomas and require the most frequent surveillance. The standard medical imaging technique for identifying glioma disease progression is by the use of magnetic resonance imaging (MRI). Computerized tomography (CT) is utilized in acute assessments and when MRI is unavailable or contraindications are present. MRI is a reliable and minimally invasive form of radiography that has been used for decades to diagnose and stage cancers, among a wide range of other applications. For individuals diagnosed with a high grade glioma, MRIs can be performed as frequently as every two months per standard of care for tumor surveillance. Although MRIs have been proven to be a safe form of radiography (if proper procedures are

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followed), they are very expensive, time consuming and can be somewhat uncomfortable for patients due to the loud noise and confined space. Additionally, high grade gliomas can be infiltrative at a microscopic level. Patients can clinically deteriorate without a clear radiographic correlate that suggests tumor progression. As such, alternative assessment measures that may identify progression and that minimize the number of MRIs these patients receive may be beneficial.

A recent study conducted by Meyers and Hess taking a look at cognitive deterioration in patients with recurrent brain tumors suggested a pattern of brain function decline approximately 6 weeks before radiographic evidence of tumor progression. This study utilized a battery of standardized psychometric tests for assessing a broad range of cognitive function (12). The idea of identifying cognitive deterioration before disease progression is diagnosed radiographically is an area of great interest for the neuro-oncology community because the timing could offer additional treatment options that may positively impact a patient's quality of life. Although, the MoCA was not one of the assessment measures used in the aforementioned study, its sensitivity and proven ability to identify mild cognitive impairment may be useful in a similar fashion for patients with high grade glioma. Any validated form of advanced warning for this patient population could potentially provide opportunities for earlier treatment and better disease control.

The main campus of the largest medical center in West Michigan is located in downtown Grand Rapids. It is called Spectrum Health and it has a growing neuro-oncology multidisciplinary clinic known as the Spectrum Health Brain and Spine Tumor Center. The physicians at this facility, like many other institutions, already use MRIs routinely to assess disease progression for high grade glioma patients. Interestingly enough, one other evaluation tool that they use with this population is the MoCA. The use of MoCAs was initiated in this clinic around September of 2013 to quantitatively gauge observed cognitive declines in patients with brain tumors. It was selected as the preferred psychometric test because it is quick, easy to administer, cost effective and non-invasive. There is now a large collection of readily available data from MoCAs that could be compared with data from routine MRIs or the occasional CT. This data could be used to conduct a study to evaluate whether MoCAs could be adopted as a reliable, early identifier of disease progression and thereby limit the burden of radiographic imaging in the high grade glioma population.

6. **Setting of the Research:** Research will consist of electronic medical record (EMR) data abstraction. The data abstraction will take place at the Spectrum Health Medical Center; however, mobile access to electronic medical record software with the proper security access may be utilized. There are no plans for any research interaction with subjects as we will be requesting permission to collect data on eligible subjects via a waiver of consent and Health Insurance Portability and Accountability Act (HIPAA) authorization.

7. **Resources Available to Conduct this Research:** For purposes preparatory to research, a preliminary report was executed by Spectrum Health Information Services (IS) to provide us a general idea of the current patient population numbers. High grade glioma diagnosis codes were used in combination with a date range dictated by the initiation of the MoCA as a standardly used assessment in the Spectrum Health Brain and Spine Tumor Center. As of a March 2017 report, it was estimated that 271 patients exist that have a moderately high potential of meeting study criteria. Even after taking into account that many potential subjects will screen fail following evaluation of all eligibility criteria, the expected volume of eligible subjects should be sufficient in achieving our goal of 128 enrolled subjects (for more

info on the enrollment goal, see Statistical Plan: Sample Size Determination) under a waiver of consent and HIPAA authorization.

Study personnel will include a principal investigator, sub-investigators and research staff. The principal investigator role will be represented by a neuro-oncologist with research experience. The principal investigator will oversee and participate in all aspects of study management (including quality checks and data analysis). In addition, the principal investigator will be a crucial point of contact for research staff in regards to study related questions. Sub-investigators will maintain the same responsibilities as the principal investigator, except for study oversight. Research staff responsibilities will include anything delegated by the principal investigator that is within the research staff member's scope of practice. Research staff may include research nurses, research coordinators, research assistants or other delegated staff. Regardless of title, all research staff will be trained per Spectrum Health Office of Research Administration (SHORA) requirements and will possess a vast and diverse research background. Any research staff (e.g., delegated staff) lacking in experience will be properly mentored on their delegated task by a skilled researcher.

For screening purposes only, study personnel will make use of the screening log, enrollment log and database from the Glioma Data Registry for Research (details can be found under Study Design: Inclusion and Exclusion Criteria). All personnel will be utilizing Spectrum Health electronic medical records (e.g., Cerner, EPIC, etc.) which can be accessed anywhere on Spectrum Health campuses or via authorized mobile access. Other software programs (e.g., OncoEMR/VIPR, the Cancer Registry, etc.) may also be utilized by the research staff to obtain further medical information, if needed. Lastly, Research Electronic Data Capture (REDCap), a secure online database will be made available to all study personnel involved with data abstraction.

8. **Study Design:**
   A. Recruitment Methods
      Subjects will be identified with the help of Spectrum Health IS in the form of a report built to flag potential subjects. Spectrum Health IS will utilize variables such as age, diagnosis codes, date ranges, etc. to filter the potential subject list to a size that is manageable. From there, the EMR of each individual subject on the list will be sequentially screened for eligibility until the sample size of 128 subjects is met (for more info on the sample size see Statistical Plan: Sample Size Determination).

   B. Inclusion and Exclusion Criteria
      The medical record from each potential subject identified will be individually and sequentially screened for eligibility utilizing the EMR. To allow for a more efficient screening process, we will also be requesting to utilize the screening log, enrollment log and REDCap data from the Glioma Data Registry for Research (IRB#: 2016-034). Two investigators (Sherman & Laney) already participate as research personnel on this registry and realize the benefit this data could be in the preparatory to research screening process for the MoCA study. The data registry contains strictly data available within the EMR, so nothing we wouldn't already be seeking access to. The use of these tools could, however, create a shortcut to rule out patients that don't fit criteria for the MoCA study without having to perform an in depth investigation in the EMR. These tools would solely be used for preparatory screening. Any subjects that look to pass all screening checks would then be examined in much more depth within the EMR to confirm eligibility until the

enrollment goal of 128 subjects is reached (for more info on the sample size, see Statistical Plan: Sample Size Determination).

The start date of the data collection window for this retrospective chart review is September 1, 2013, which is the estimated time when MoCAs were initiated into practice at the Spectrum Health Brain and Spine Tumor Center. The concluding date for the data collection window will be the date of institutional review board (IRB) approval of this research.

Inclusion Criteria:
- Adults $\geq$ 18 years of age.
- Pathology diagnosis of a high grade glioma (WHO grade III or IV). Grade III pathologies include, but are not limited to, anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic mixed glioma (also referred to as anaplastic oligoastrocytoma). Grade IV pathologies include, but are not limited to, glioblastoma, gliosarcoma and gliomatosis cerebri.
- Surgical resection or biopsy of high grade glioma with post-op or post-biopsy radiation treatment.
- At least one instance of disease progression.
- Completion of a minimum of three MoCAs (baseline MoCA must be subsequent to high grade glioma resection or biopsy with post-op or post-biopsy radiation, concluding MoCA for purposes of this study must be at the first instance of disease progression and a minimum of one MoCA must be reported in between).

Exclusion Criteria:
- Individuals < 18 years of age at the time of high grade glioma pathology diagnosis.
- History of dementia.

C. Study Endpoints
Specific Aim 1: Determine whether there is a statistically significant decline in MoCA scores from a predetermined baseline to disease progression. MoCAs subsequent to high grade glioma resection or biopsy with post-op or post-biopsy radiation will be considered as the baseline MoCA for all eligible subjects. These scores in comparison with the MoCA scores that coincide with disease progression will be tested via a paired t-test (presuming statistical assumptions are met). Disease progression will be determined by a physician (neurology) in the form of their dictation in the subjects' EMR following their review of radiographic imaging (e.g., MRI, CT, etc.) and/or the radiographic imaging report. For study purposes, the date of disease progression will be the date the radiographic imaging occurred, not the date it was dictated in the EMR. If specific aim 1 indicates a significant decline, we will proceed to specific aim 2.

Specific Aim 2: Determine the average time point between baseline and disease progression where MoCA scores see the largest magnitude of change between consecutive assessments. For each eligible subject, the date of the MoCA that follows the largest magnitude of change in score from its preceding MoCA will be identified. This date will be subtracted from the date of disease progression. The resulting number of days will then be averaged across subjects. This will help

determine how much earlier, in days, disease progression can be detected on a MoCA versus radiographic imaging.

D. Procedures Involved in the Research

This will be a retrospective chart review conducted at Spectrum Health under a waiver of consent and HIPAA authorization. The intended duration of the research, assuming the enrollment goal is feasible, is less than one year.

Once the research study is IRB approved, potential subjects will be identified with the help of Spectrum Health IS and then individually screened for eligibility. Once a screened subject has met all eligibility criteria, that subject is considered enrolled in the study and will be assigned a unique study identification number to maintain confidentiality. A study correlation tool will be utilized to link subjects to their study number. This will be kept securely on Spectrum Health's network drive.

Retrospective data will be collected from the EMR systems available at Spectrum Health. All data will be stored in an online database known as REDCap that will only be accessible by IRB approved personnel. For enrolled subjects, delegated research staff will access REDCap and enter the "ONC – MoCA Study" project. Within the project, there will be a series of data collection instruments built specifically for this research to capture all relevant data (see Appendix B for an example of the REDCap data collection tool). Once all subject data has been collected, it will be exported from REDCap and a statistical analysis will ensue. In addition to testing the specific aims and providing summary statistics, a selection of the retrospective data points will be tested as potential confounding variables that may impact the difference in MoCA scores between baseline and disease progression (see Statistical Plan: Statistical Methods for more details). Results will be presented in detail in a thesis with intentions to condense to a manuscript suitable for publication in a peer reviewed journal.

E. Data Management

Collected data will include a variety of information in relation to the following topics: demographics, tumor characteristics, pathology, imaging type, surgery type, treatment, medication, MoCA scores, Patient Health Questionnaire - 9 (PHQ-9) scores, mortality, disease progression and specific dates (e.g., diagnosis, progression/imaging, surgery, MoCA, expiration, radiation, etc.). Data will be stored in the REDCap online database. REDCap is a secure web system that not only requires a password log-in, but Spectrum Health has to individually, grant authorized access to REDCap through their account. Any other electronic study files (e.g., enrollment log, study correlation tool, etc.) will be kept on Spectrum Health's secure network drive. Paper records (e.g., regulatory documents, etc.) will be stored in secure locked cabinets within the Spectrum Health Office of Research Administration.

F. Withdrawal of Subjects

Due to study design (retrospective chart review with a waiver of consent and HIPAA authorization), we do not foresee any possibility of encountering a request by a subject to be withdrawn. The principal investigator can however remove a subject from the study if it is felt necessary to preserve the integrity of the data. In an instance such as this, a valid reason for removal must be documented and all efforts

should be made to erase/delete/destroy any data collected on that particular subject up to that point. In addition, no further data would be collected on this subject.

9. **Statistical Plan:**
    A. <u>Statistical Methods</u>

    Data will be analyzed using Statistical Analysis System (SAS) Enterprise Guide Version 7.1. Summary statistics will be provided. Quantitative data will be expressed using means and standard deviations. Qualitative data will be expressed as frequency and percentages.

    To test the difference in MoCA scores between baseline and disease progression as described in specific aim 1, we are planning to use a parametric paired t-test since the outcome of the MoCA score is continuous and the pre and post scores are dependent observations. In essence, we will take the average of each patient's (baseline MoCA score – disease progression MoCA score) and compare that to zero. Then we will determine if that difference is significant or not. A nonparametric Wilcoxon Signed Rank test will be used if the assumption of normality is not met.

    Determining the average time point between baseline and disease progression where MoCA scores see the largest magnitude of change between consecutive assessments will be calculated using SAS as well, but will not require a statistical test. Rudimentary calculations as described in specific aim 2 will be sufficient in achieving the result. There are, however, a few exceptions to the rule. Any subject that has an equal magnitude of change between all MoCA scores (steady slope) will be excluded from the sample used to calculate specific aim 2. When identifying the largest magnitude of change for each subject, only those changes where scores are declining will be acceptable. Lastly, when identifying the largest magnitude of change for a particular subject, there could be multiple occurrences between baseline and disease progression which are equal in magnitude and the largest. If this is the case, the date of the MoCA with the largest magnitude of change from its preceding MoCA and that is closest to baseline will be utilized for the data point for that particular subject.

    Additional statistical testing will occur on a variety of other demographic groupings of interest to identify confounding variables that may impact, positively or negatively, the difference in MoCA scores between baseline and disease progression. Distinguishing these factors may help identify demographic groupings with higher possibilities of false positives/negatives affecting the reliability of the MoCA in early identification of disease progression. To test the average difference in MoCA scores between baseline and disease progression in determining if there is a difference between (demographic groupings) we are planning to use a series of parametric two sample independent t-tests since the outcome of the difference in MoCA scores is continuous and the (demographic groupings) are all independent groups. Essentially, we are comparing two groups to see if there is a significant difference between them. If so, the variable is a confounder. A nonparametric Wilcoxon Rank Sum test will be used if the assumption of normality is not met. The following is a list of each demographic grouping and how each variable will be defined.
    - Age: Subjects will be divided into two age groups. Those 18-59 years of age and those $\geq$ 60 years of age at disease progression.
    - Tumor Grade: Subjects will be divided into two groups. Those who were diagnosed at resection or biopsy with a WHO grade III tumor and those who

were diagnosed at resection or biopsy with a WHO grade IV tumor.

- Chemotherapy: Subjects will be divided into two groups. Those who were being treated with chemotherapy at the time of disease progression and those who were not being treated with chemotherapy at the time of disease progression. For purposes of this research study, chemotherapy will be defined by the following medications: Temodar (Temozolomide), Avastin (Bevacizumab), Ceenu (Lomustine), Opdivo (Nivolumab), Keytruda (Pembrolizumab), Paraplatin (Carboplatin) and Camptosar (Irinotecan).
- Stimulants: Subjects will be divided into two groups. Those who were being treated with stimulants at the time of disease progression and those who were not being treated with stimulants at the time of disease progression. For purposes of this research study, stimulants will be defined by the following medications: Provigil (Modafinil), Nuvigil (Armodafinil), Ritalin (Methylphenidate), Adderall (Amphetamine/Dextroamphetamine) and Vyvanse (Lisdexamfetamine).
- Antidepressants: Subjects will be divided into two groups. Those who were being treated with antidepressants at the time of disease progression and those who were not being treated with antidepressants at the time of disease progression. For purposes of this research study, antidepressants will be defined by the following medications: Lexapro (Escitalopram), Prozac (Fluoxetine), Celexa (Citalopram), Cymbalta (Duloxetine), Effexor (Venlafaxine) and Zoloft (Sertraline).
- Anti-Epileptic Drugs: Subjects will be divided into two groups. Those who were being treated with anti-epileptic drugs at the time of disease progression and those who were not being treated with anti-epileptic drugs at the time of disease progression. For purposes of this research study, anti-epileptic drugs will be defined by the following medications: Keppra (Levetiracetam), Vimpat (Lacosamide), Lamictal (Lamotrigine), Topamax (Topiramate), Trileptal (Oxcarbazepine), Tegretol (Carbamazepine), Dilantin (Phenytoin), Depakote (Valproic Acid) and Zonegran (Zonisamide).

One final area of interest will be determining if there is a correlation between depression and the difference in MoCA scores between baseline and disease progression. A correlation is a measure of how things are related, so understanding the strength and direction of this relationship, if one exists, would provide further awareness of the impact of depression on the reliability of the MoCA being used as an early identifier of disease progression. Depression will be quantified by utilizing scores from a routinely used depression screening tool known as the PHQ-9 (see Appendix C for an example of a Spectrum Health modified version of the Pfizer Inc. questionnaire). Depression will be defined as the PHQ-9 score at disease progression. To test if there is a correlation between the depression screening tool scores and the difference in MoCA scores between baseline and disease progression, a Pearson correlation test will be used since both variables are continuous. The Pearson correlation test will result in a value ranging anywhere from -1 to 1, where 0 represents no correlation. A value of -1 represents a perfect negative correlation or in terms specific to the study, it would confirm that as depression worsens, MoCA scores would become more abnormal. On the other end of the spectrum, a value of 1 represents a perfect positive correlation or in study specific terms, a confirmation that as depression worsens, MoCA scores would become more normal. In effect, a very strong relationship in either direction would

represent something similar to a confounder. It should not be necessary to utilize the nonparametric Spearman's rank correlation in this instance.

    B. <u>Sample Size Determination</u>
The sample size required to accomplish our specific aims with a standard power level of 0.8 will be 34 subjects; however, to test the additional statistical models described above at a power of 0.8 we will need to increase that number to 128 subjects. Our study goal will be to attain 128 subjects to maximize our power to the standard level. If the goal of 128 subjects is not achievable within the parameters and constraints surrounding the conduct of the study, the objective will be to maximize the sample size while being sure to surpass 34 subjects. Maximizing the sample size will consequentially elevate the power level to as near 0.8 as possible. Significance will be set at the standard level of 0.05.

10. **Anticipated Outcomes:** There is currently no available data to support or oppose the use of MoCAs as an early indicator of disease progression in the high grade glioma population as this is a novel concept. We can, however, draw inference from past studies in our anticipated outcomes. We know that standardized psychometric instruments used for assessing cognitive function with previously published evidence of validation and reliability have demonstrated an ability to identify cognitive decline approximately 6 weeks in advance of radiographic evidence of disease progression in patients with recurrent malignant glioma (12). We also know that the MoCA has been validated in its exemplary ability to identify mild cognitive impairment when tested alongside the Mini-Mental State Examination (MMSE). Both assessments demonstrated high percentages in specificity, but where the MoCA really stood out was in sensitivity. The MoCA was able to identify 90% of the mild cognitive impaired subjects from the sample population compared to the MMSE's 18% (2).The validation of the MoCA's ability to assess cognitive function at a comparable level to other standardized tests suggests that the MoCA may demonstrate similar results to the Meyers and Hess study if tested in a complementary fashion (12).

We anticipate based on inference from past studies and prior anecdotal evidence that specific aim 1 will show a statistically significant decline in MoCA scores from baseline to disease progression. In specific aim 2, we predict that the average time point between baseline and disease progression where MoCA scores see the largest magnitude of change between consecutive assessments will be approximately 60 days prior to disease progression. 60 days was chosen as the anticipated outcome due to the limitations in frequency of routinely administered MoCAs in the setting of this research. The Spectrum Health Brain and Spine Tumor Center only performs MoCAs at the time of radiographic imaging, thus the shortest duration between sequential imaging/MoCAs for routine observation of a high grade glioma is roughly 60 days. This would be the MoCA closest in proximity to the 6 week mark, which was proven to be the time point where disease progression could be identified from psychometric tests in the Meyers and Hess study (12).

In regards to the testing of demographic groupings, we do feel there is potential for us to uncover a confounding variable that could influence the difference in MoCA scores between baseline and disease progression. If any of the demographic groupings are identified as a confounder, the bulleted list below describes for each grouping what we anticipate its influence will be on MoCA scores in either positive or negative directions and our justification for that prediction.

- Age: Individuals who are advanced in age are at an increased risk for cognitive impairment and decline, therefore they may be more susceptible to cognitive decline associated with tumor progression and diminished MoCA scores.
- Tumor Grade: Grade IV tumors are more aggressive and infiltrative, which may be associated with considerable cognitive decline and inferior MoCA scores.
- Chemotherapy: Treatment such as chemotherapy can cause fatigue, which could negatively affect MoCA scores.
- Stimulants: The ability of these types of medications to increase focus may enhance performance on MoCA testing.
- Antidepressants: The ability of these types of medications to alleviate symptoms of depression, anxiety, etc. may improve MoCA scores.
- Anti-Epileptic Drugs: Medication may cause cognitive slowing and lower MoCA scores.

Lastly, we will be determining if there is a correlation between depression and the difference in MoCA scores between baseline and disease progression. We anticipate a negatively correlated relationship due to commonly known effects of depression such as low mood, anxiety and fatigue adversely influencing MoCA scores.

If our anticipated outcomes are confirmed and other future research within the neuro-oncology community validates our results, MoCAs could become a universally accepted standard practice within neuro-oncology clinics around the country and possibly the world. In instances where radiographic evidence of disease progression is questionable, a MoCA would be able to provide a valid second method of diagnosis. MoCAs have the potential to reduce the frequency of radiographic imaging and all the unfavorable consequences associated with it, such as time, expense, loud noise, confined space and even radiation when receiving a CT scan. If MoCAs do provide reliable early identification of high grade glioma disease progression, then the opportunity exists for physicians to grant early treatment for better disease control. For a population with such a poor prognosis and limited quality of life, any advances can make a big difference when viewed from this population's perspective.

11. **Risks to Subjects:** Because the research involves only the collection of data, participation in this registry carries no additional risks to subjects other than the possible loss of confidentiality of personal health information. Every effort will be made for data provided as part of the research to be kept confidential by the research staff. Any other research related risks are currently unforeseeable.

12. **Potential Benefits to Subjects:** There is no anticipated benefit to subjects enrolled in the research; however, the information gained from the research could help others in the future.

13. **Provisions to Protect the Privacy Interests of Subjects:** In an effort to protect the privacy of subjects, an IRB approved waiver of consent and HIPAA authorization will be requested to accommodate a retrospective chart review of eligible subjects under the oversight of the Spectrum Health Human Research Protection Program.

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14. **Provisions to Maintain the Confidentiality of Data:** Information about subjects will be kept confidential and managed according to the requirements of the HIPAA. All electronic data will be kept in secure password protected locations. Only the investigators participating on this registry and the study staff will have access. Any paper records will be stored in secure locked cabinets maintained by the study staff. In an effort to align with site retention guidelines, study documentation will be retained for seven years following study closure, which is the maximum length of retention for any document in a study where all data is abstracted from clinical records. Upon completion of the retention period, all retained study documentation will be deleted or destroyed in accordance with Spectrum Health documentation destruction policies.

15. **Cost to Subjects:** Patients or their third party payer/insurance carrier (if applicable) will not incur any charges associated with research data acquisition, storage or its subsequent use.

16. **Consent Process:** We are requesting a waiver of consent and HIPAA authorization. Because the registry is solely data collection, risk is minimized to the potential loss of confidential health information. This risk is not increased under the waiver of consent and HIPAA authorization. Safeguards remain in place to minimize this risk in an effort to protect the rights and welfare of all participants. The following information is a justification for our request for waiver and HIPAA authorization:

    The targeted population of high grade glioma patients is very limited as it stands. In addition, the study requires subjects to have completed at least three MoCAs, which is an assessment that was only implemented as standard practice within the Spectrum Health Brain and Spine Tumor Center approximately four years ago (September 2013). This cuts our already limited population to only a four year window. Finally, the high grade glioma population has a very poor prognosis with subjects living sometimes less than a year from diagnosis, so the majority of these subjects will be expired.

    To further vindicate our request, a preparatory to research report was run in March of 2017 to provide an estimate on actual population within the Spectrum Health system. Using only dates and diagnoses as filters, we arrived at 271 potential subjects. A significant amount of these subjects will not end up being eligible once all criteria are taken into account, leaving little room for subjects to forgo participation even if we had the ability to consent all the subjects, which is inherently not possible due to the life expectancy of this diagnosis. With all factors considered, we do not see this study being feasible (enrollment goal of 128) or safeguarded from skewed data (due to an extremely limited population) without a waiver of consent and HIPAA authorization.

17. **Vulnerable Populations:** There are no vulnerable populations specifically targeted for this research. Children and neonates will definitely be excluded, but the following vulnerable populations could be enrolled if criteria are met: adults with diminished decision making capabilities, limited English proficiency/non-English speakers, non-readers/visually impaired individuals, pregnant women/fetuses and prisoners. The justification for including these vulnerable populations in the study is because there will be no subject interaction under the waiver of consent and HIPAA authorization, which eliminates any opportunity for coercion or undue influence. In addition, this is a minimal risk study involving only data collection, so these vulnerable populations are not being exposed to any increased risk because of their vulnerability nor is their vulnerability affecting the intentions of the protocol.

18. **Sharing of Results with Subjects:** There are no plans to share research data with subjects as all information being collected comes directly from their personal medical record. If a subject would like information within their own medical record, they will be instructed to contact the Release of Information Office within Spectrum Health's Heath Information Management department.

19. **References:**

1) About [Internet]. MoCA Montreal - Cognitive Assessment. [cited 2017 Feb 18]. Available from: http://www.mocatest.org/about/

2) Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. J Am Geriatr Soc. 2005 Apr 1;53(4):695–9.

3) Julayanont P, Brousseau M, Chertkow H, Phillips N, Nasreddine ZS. Montreal Cognitive Assessment Memory Index Score (MoCA-MIS) as a Predictor of Conversion from Mild Cognitive Impairment to Alzheimer's Disease. J Am Geriatr Soc. 2014 Apr 1;62(4):679–84.

4) MoCA Test Full [Internet]. MoCA Montreal - Cognitive Assessment. [cited 2017 Feb 18]. Available from: http://www.mocatest.org/paper-tests/moca-test-full/

5) FAQ [Internet]. MoCA Montreal - Cognitive Assessment. [cited 2017 Feb 18]. Available from: http://www.mocatest.org/faq/

6) Brain Tumor Statistics | American Brain Tumor Association [Internet]. [cited 2017 Feb 5]. Available from: http://www.abta.org/about-us/news/brain-tumor-statistics/

7) Chang HJ, Burke AE, Glass RM. Gliomas. JAMA. 2010 Mar 10;303(10):1000–1000.

8) Reyes-Botero G, Mokhtari K, Martin-Duverneuil N, Delattre J-Y, Laigle-Donadey F. Adult Brainstem Gliomas. The Oncologist. 2012 Mar;17(3):388–97.

9) Diffuse Intrinsic Pontine Glioma [Internet]. [cited 2017 Feb 5]. Available from: https://www.stjude.org/disease/diffuse-intrinsic-pontine-glioma.html

10) Glioma | American Brain Tumor Association [Internet]. [cited 2017 Feb 5]. Available from: http://www.abta.org/brain-tumor-information/types-of-tumors/glioma.html

11) Kieffer S. Brain Tumor Grading System | Johns Hopkins Comprehensive Brain Tumor Center [Internet]. [cited 2017 Feb 6]. Available from: http://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/brain_tumor/diagnosis/brain-tumor-grade.html

12) Meyers CA, Hess KR. Multifaceted end points in brain tumor clinical trials: cognitive deterioration precedes MRI progression. Neuro-Oncol. 2003 Apr;5(2):89–95.

13) phqscreeners [Internet]. phqscreeners. [cited 2017 Apr 1]. Available from: http://www.phqscreeners.com/

20. Attachments:
- Appendix A: Version 7.1 of the Montreal Cognitive Assessment (4).
- Appendix B: REDCap data collection tool.
- Appendix C: Spectrum Health modified version of Pfizer Inc.'s Patient Health Questionnaire - 9. Unaltered versions are publically available online (13).

Appendix E

- Spectrum Health IRB approval letter dated August 11, 2017 (initial submission).
- GVSU IRB deferral letter dated August 25, 2017.
- Spectrum Health IRB approval letter dated September 8, 2017 (modification).

APPROVAL OF RESEARCH

August 11, 2017

Wendy Sherman MD
Spectrum Health
25 Michigan Street NE
Grand Rapids, MI 49503

TYPE OF REVIEW: **Initial, Non-Committee Review**

IRB#: **2017-187** *(please reference this number in all correspondence with the IRB)*

PROTOCOL NAME: **Use of the Montreal Cognitive Assessment as an Early Indicator of Tumor Progression in Patients with Stage III and IV Gliomas**

SPONSOR: **Investigator**

Dear Dr. Sherman:

The above referenced protocol and associated materials were reviewed and approved by the IRB via expedited review on August 11, 2017 under category 5 as described in 45 CFR 46.110.

The approval period for this research is from **August 11, 2017** to **August 10, 2018.**

The IRB reviewed the following documents related to the approval of the research proposal:
- Initial application signed 07/27/2017
- Study protocol dated 07/27/2017
- Data collection sheet dated 07/27/2017
- Patient Health Questionnaire (PHQ-9) dated 06/16
- Montreal Cognitive Assessment (MoCA) version 7.1

The IRB made the following determinations:

1. **WAIVER OF CONSENT/HIPAA AUTHORIZATION**: A waiver of consent has been approved per 45 CFR 46.116(d) and a waiver of HIPAA authorization has been approved per 45 CFR 164.512(i)(2)(ii).

2. **RESEARCH UNDER AN IRB RELIANCE AGREEMENT**: The IRB agreed to conduct this study under the terms of the Spectrum Health and Grand Valley State University (GVSU) IRB Reliance Agreement. The GVSU IRB will by relying on Spectrum Health IRB for this study and Spectrum Health IRB will serve as the IRB of record. As part of this agreement, Spectrum Health IRB will share with the relying IRB the initial IRB approval letter, any new relevant information and documents during the course of the study, and any changes to study IRB approval status.

Any changes made to the study following this approval, including informed consent changes, require submission in writing to the IRB and approval by the committee. Changes may not be implemented until approved by the IRB except when necessary to eliminate apparent immediate hazards to the subject.

Approval of your research means you are responsible for complying with all applicable policies and procedures of the FDA, OHRP, HIPAA, Spectrum Health, and the Spectrum Health IRB. Also, please be advised that unanticipated problems involving risk to subjects or others must be *promptly* reported to the IRB. You may reference the Investigator Manual for guidance on expectations of the IRB after approval.

Please be advised, this approval letter is limited to Spectrum Health IRB review and you will still need GVSU IRB approval. It is your responsibility to ensure all necessary institutional permissions are obtained prior to beginning this research. This includes, but is not limited to, ensuring all contracts have been executed, any necessary Data Use Agreements and Material Transfer Agreements have been signed, documentation of support from the Department Chief has been obtained, and any other outstanding items are completed (i.e. CMS device coverage approval letters, material shipment arrangements, etc.).

The IRB requires submission of the Continuing Review Progress Report or Study Completion Notification to the committee prior to the study expiration date. It is recommended you submit this xform 4-6 weeks prior to the expiration date to allow time for processing. Your study approval expires on **August 10, 2018 at 11:59pm** and cannot continue until re-approved by the Spectrum Health IRB. If your study has been completed, terminated, or if you do not wish to continue, please submit the Study Completion Notification before the expiration date.

If you have any questions please contact the Spectrum Health IRB office at 616-486-2031, email irbassist@spectrumhealth.org, or visit us on the web at www.spectrumhealth.org.

Sincerely,

Jeffrey Jones MD
Chair, Spectrum Health IRB

cc: Eric Laney BS, GVSU IRB

DATE: August 25, 2017

TO: Debra Burg, Ph.D
FROM: Grand Valley State University Human Research Review Committee
STUDY TITLE: [1114271-1] Use of the Montreal Cognitive Assessment as an Early
                         Indicator of Tumor Progression in Patients with Stage III and IV
                         Gliomas
REFERENCE #:   18-029-H
SUBMISSION TYPE: New Project

ACTION: DEFERRED
EFFECTIVE DATE: August 25, 2017
REVIEW TYPE: Administrative Review

Thank you for your submission of materials for your planned research study. It has been determined that this project is a DEFERRAL.

The study was reviewed by Spectrum Health Institutional Review Board (IRB; Protocol # 2017-187) on August 11, 2017, and was determined to be COVERED human subjects research* according to current federal regulations. The study meets eligibility for expedited determination under category 5, 45 CFR 46.110.

Any research-related problem or event resulting in a fatality or hospitalization requires immediate notification to the Human Research Protections Administrator, Dr. Jeffrey Potteiger, Office of Graduate Studies (616)331-7207. See *HRRC policy 1020, Unanticipated problems and adverse events.*

If you have any questions, please contact the Office of Research Integrity and Compliance at (616) 331-3197 or rci@gvsu.edu. Please include your study title and reference number in all correspondence with our office.

*Research is a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (45 CFR 46.102 (d)).

Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains: data through intervention or interaction with the individual, or identifiable private information (45 CFR 46.102 (f)).

Scholarly activities that are not covered under the Code of Federal Regulations should not be described or referred to as *research* in materials to participants, sponsors or in dissemination of findings.

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APPROVAL OF RESEARCH

September 8, 2017

Wendy Sherman MD
Spectrum Health
25 Michigan Street NE
Grand Rapids, MI 49503

TYPE OF REVIEW: **Modifications, Non-Committee Review**

IRB#: **2017-187** *(please reference this number in all correspondence with the IRB)*

PROTOCOL NAME: **Use of the Montreal Cognitive Assessment as an Early Indicator of Tumor Progression in Patients with Stage III and IV Gliomas**

SPONSOR: **Investigator**

Dear Dr. Sherman:

The request for modification of approved human research and associated materials were reviewed and approved on September 8, 2017.

As a reminder, IRB approval for this research expires on **August 10, 2018.**

The IRB reviewed the following documents related to the approval of the modification:
- Modification of Approved Research xform signed August 30, 2017
- Data collection tool dated 8/30/17

If you have any questions please contact the Spectrum Health IRB office at 616-486-2031, email irbassist@spectrumhealth.org, or visit us on the web at www.spectrumhealth.org.

Sincerely,

Jeffrey Jones MD
Chair, Spectrum Health IRB

cc: Eric Laney BS

HRP-515

Bibliography/References

1. Wen PY, Kesari S. Medical Progress: Malignant Gliomas in Adults. N Engl J Med. 2008 Jul 31;359(5):492–507.

2. Glioblastoma (GBM) | American Brain Tumor Association [Internet]. [cited 2017 Sep 16]. Available from: http://www.abta.org/brain-tumor-information/types-of-tumors/glioblastoma.html

3. Henson JW. Glioblastoma Multiforme and Anaplastic Gliomas: A Patient Guide [Internet]. 1999. Available from: https://brain.mgh.harvard.edu/patientguide.htm

4. Meyers CA, Hess KR. Multifaceted end points in brain tumor clinical trials: cognitive deterioration precedes MRI progression. Neuro-Oncol. 2003 Apr;5(2):89–95.

5. Neugroschl J, Wang S. Alzheimer's Disease: Diagnosis and Treatment Across the Spectrum of Disease Severity. Mt Sinai J Med N Y. 2011;78(4):596–612.

6. Cordell CB, Borson S, Boustani M, Chodosh J, Reuben D, Verghese J, et al. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. Alzheimers Dement. 2013 Mar;9(2):141–50.

7. About [Internet]. MoCA Montreal - Cognitive Assessment. [cited 2017 Feb 18]. Available from: http://www.mocatest.org/about/

8. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. J Am Geriatr Soc. 2005 Apr 1;53(4):695–9.

9. Julayanont P, Brousseau M, Chertkow H, Phillips N, Nasreddine ZS. Montreal Cognitive Assessment Memory Index Score (MoCA-MIS) as a Predictor of Conversion from Mild Cognitive Impairment to Alzheimer's Disease. J Am Geriatr Soc. 2014 Apr 1;62(4):679–84.

10. Julayanont P, Phillips N, Chertkow H, Nasreddine ZS. Montreal Cognitive Assessment (MoCA): Concept and Clinical Review. In: Cognitive Screening Instruments. 111-152: Springer-Verlag; 2013.

11. Tang-Wai DF. Cognitive Testing and Localization Made Ridiculously Simple [Internet]. 26th Annual Geriatric Refresher Day; 2012 May 2; University of Western Ontario, London ON. Available from: https://www.sjhc.london.on.ca/sites/default/files/pdf/grid_workshop_2.pdf

12. MoCA Test Full [Internet]. MoCA Montreal - Cognitive Assessment. [cited 2017 Feb 18]. Available from: http://www.mocatest.org/paper-tests/moca-test-full/

13. FAQ [Internet]. MoCA Montreal - Cognitive Assessment. [cited 2017 Feb 18]. Available from: http://www.mocatest.org/faq/

14. Brain Tumor Statistics | American Brain Tumor Association [Internet]. [cited 2017 Feb 5]. Available from: http://www.abta.org/about-us/news/brain-tumor-statistics/

15. Chang HJ, Burke AE, Glass RM. Gliomas. JAMA. 2010 Mar 10;303(10):1000–1000.

16. Reyes-Botero G, Mokhtari K, Martin-Duverneuil N, Delattre J-Y, Laigle-Donadey F. Adult Brainstem Gliomas. The Oncologist. 2012 Mar;17(3):388–97.

17. Diffuse Intrinsic Pontine Glioma [Internet]. [cited 2017 Feb 5]. Available from: https://www.stjude.org/disease/diffuse-intrinsic-pontine-glioma.html

18. Glioma | American Brain Tumor Association [Internet]. [cited 2017 Feb 5]. Available from: http://www.abta.org/brain-tumor-information/types-of-tumors/glioma.html

19. Kieffer S. Brain Tumor Grading System | Johns Hopkins Comprehensive Brain Tumor Center [Internet]. [cited 2017 Feb 6]. Available from: http://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/brain_tumor/diagnosis/brain-tumor-grade.html

20. Phqscreeners [Internet]. phqscreeners. [cited 2017 Apr 1]. Available from: http://www.phqscreeners.com/

21. Wefel JS, Cloughesy T, Zazzali JL, Zheng M, Prados M, Wen PY, et al. Neurocognitive function in patients with recurrent glioblastoma treated with bevacizumab. Neuro-Oncol. 2011 Jun 1;13(6):660–8.

22. Rooney AG, Carson A, Grant R. Depression in Cerebral Glioma Patients: A Systematic Review of Observational Studies. JNCI J Natl Cancer Inst. 2011 Jan 5;103(1):61–76.

23. REDCap [Internet]. [cited 2018 Feb 26]. Available from: https://www.project-redcap.org/