Evidence of increased brain amyloid in severe TBI survivors at 1, 12, and 24 months after injury: report of 2 cases

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Traumatic brain injury (TBI) is a major risk factor for Alzheimer's disease. With respect to amyloid deposition, there are no published serial data regarding the deposition rate of amyloid throughout the brain after TBI. The authors conducted serial ¹⁸F-AV-45 (florbetapir F18) positron emission tomography (PET) imaging in 2 patients with severe TBI at 1, 12, and 24 months after injury. A total of 12 brain regions were surveyed for changes in amyloid levels.

Case 1 involved a 50-year-old man who experienced a severe TBI. Compared with the 1-month time point, of the 12 brain regions that were surveyed, a decrease in amyloid (as indicated by standard uptake value ratios) was only observed in the hippocampus (−16%, left; −12%, right) and caudate nucleus (−18%, left; −18%, right), suggesting that initial amyloid accumulation in the brain was cleared between time points 1 and 12 months after injury. Compared to the scan at 1 year, a greater increase in amyloid (+15%) was observed in the right hippocampus at the 24-month time point. The patient in Case 2 was a 37-year-old man who suffered severe trauma to the head and a subsequent stroke; he had poor cognitive/functional outcomes and underwent 1.5 years of rehabilitation. Due to a large infarct area on the injured side of the brain (right side), the authors focused primarily on brain regions affected within the left hemisphere. Compared with the 1-month scan, they only found an increase in brain amyloid within the left anterior putamen (+11%) at 12 months after injury. In contrast, decreased amyloid burden was detected in the left caudate nucleus (−48%), occipital cortex (−21%), and precuneus (−19%) brain regions at the 12-month time point, which is indicative of early accumulation and subsequent clearance. In comparison with 12-month values, more clearance was observed, since a reduction in amyloid was found at 24 months after trauma within the left anterior putamen (−12%) and occipital cortex (−15%). Also, by 24 months, most of the amyloid had been cleared and the patient demonstrated improved results on the Rivermead symptom questionnaire, Glasgow Outcome Scale–Extended, and Disability Rating Scale. With respect to APOE status, the patient in Case 1 had two ε3 alleles and the patient in Case 2 had one ε2 and one ε3 allele.

In comparison to the findings of the initial scan at 1 month after TBI, by 12 and 24 months after injury amyloid was cleared in some brain regions and increased in others. Serial imaging conducted here suggests that florbetapir F18 PET imaging may be useful in monitoring amyloid dynamics within specific brain regions following severe TBI and may be predictive of cognitive deficits.

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KEY WORDS amyloid; florbetapir F18; traumatic brain injury

EACH year in the United States alone, about 300,000 people are hospitalized for traumatic brain injury (TBI), with a mortality rate of 16%.^{1,26} After TBI, secondary brain injury escalates due in part to heightened levels of oxidant injury, inflammation, and amyloid production. Increases in secondary brain injury may begin

almost immediately after the primary injury^{8,15} and evolve into chronic neurodegenerative conditions.

TBI is a major risk factor for the development of chronic neurodegenerative conditions such as Alzheimer's disease (AD).^{4,11,18,20,29} Postmortem analyses of brains from TBI patients have revealed that the degree of amyloid plaque

ABBREVIATIONS AD = Alzheimer's disease; DRS = Disability Rating Scale; GCS = Glasgow Coma Scale; GOS-E = Glasgow Outcome Scale–Extended; MMSE = Mini-Mental State Examination; MNI = Montreal Neurological Institute; SUVR = standard uptake value ratio; TBI = traumatic brain injury; VOI = volume of interest.

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deposition in the brain correlated with the level of cognitive impairment.^{11,16,18,20} Also, several autopsy studies have shown amyloid plaques are present in the brain as early as 2 hours after injury and persist even 2.5 years later.^{11,23,30} Furthermore, the likelihood of amyloid plaque deposition was more evident in patients with *APOE* $\epsilon 4$ expression (50% in Apo-E4-expressing patients vs 30% in the non-Apo-E4-expressing group). The Apo-E4-expressing individuals also performed worse on cognitive tests at time points more distant from the injury.^{4,19} Given the increased risk for AD noted in Apo-E4-expressing patients, the increased likelihood for amyloid plaque deposition in TBI patients with the *APOE* $\epsilon 4$ allele supports the reported link between severe TBI and AD-like dementia.¹⁹ In this study, we hypothesized that people who express Apo-E4 will accumulate more amyloid in the brain after TBI.

Recently, a single PET scan ([11C] PiB) of the head conducted within 1 year of TBI showed that amyloid deposition correlates with histological findings of amyloid plaques in the brain of people who died shortly after the lone scan.¹⁰ In this study we used ¹⁸F-AV-45 (florbetapir F18), which has a longer half-life and has a high binding affinity for fibrillar amyloid,^{3,6} as a more practical tool for imaging the head of TBI survivors. In previous AD studies, florbetapir F18 binding was characterized and found to correlate with cognitive and mood disorders.^{3,6,12,17,35}

In this prospective study, the aim was to conduct serial imaging in TBI survivors to determine the deposition profile within a number of brain regions at subacute (~30 days after injury) and chronic (12 and 24 months) time points after injury.

Case Reports

Case 1

History

This 50-year-old man had experienced a severe TBI (Glasgow Coma Scale [GCS] score of 3) due to a motor vehicle collision (Table 1). CT scans showed that he had a 3-mm midline shift. Additionally, a subdural hematoma was reported in the left frontal and temporoparietal cortex. To lower intracranial pressure, a left hemispherectomy was performed (Fig. 1A and B).

Serial Florbetapir F18 PET Imaging

Following discharge from Parkland Hospital (Dallas, Texas) the patient underwent scanning with the Siemens ECAT HR PET scanner on Day 30 after the injury, and

FIG. 1. CT scans obtained in Case 1 (A, within the first 6 hours after injury; B, postcraniotomy) and Case 2 (C, within the first 6 hours after injury; D, postcraniotomy). Arrows indicate locations of hematomas, ventricles, infarct areas, and craniotomy.

subsequent scanning was performed at 1 and 2 years after injury. To label the fibrillar amyloid, 370 MBq (10 mCi) of the florbetapir F18 tracer (AVID Radiopharmaceuticals) was injected. Following a 50-minute washout period, a 10-minute continuous brain PET scan was conducted. Images were reconstructed immediately after the 10-minute scan. We acquired individual measures of amyloid deposition for specific brain structures. A hierarchical regression technique was used to analyze the data. Images were spatially normalized to the Montreal Neurological Institute (MNI) space using SPM8 and special image templates developed for florbetapir F18 from the brains of normal controls. These values were used to extract a value of amyloid from the data. A negative scan was defined as one in which the majority of the tracer was bound in the white matter (Fig. 2A and B). Initially, the scans were analyzed for significant accumulation of tracer in the gray matter. A scan is considered positive if tracer retention is evident primarily in the cortical gray areas (Fig. 2C). After spatial normalization, volumes of interest (VOIs) that were derived from MRI data from the MNI atlas were applied using internally developed MATLAB code to extract count density from 12 brain regions (anterior and posterior cingulate gyrus, dorsolateral prefrontal cortex, frontal cortex, left and right hippocampus, left and right anterior putamen, left and right caudate nucleus, left and right thalamus, occipital cortex, orbital frontal cortex, parietal cortex, precuneus, temporal cortex). Standard uptake value ratios (SUVRs) were computed for VOIs and a cerebellar VOI was extracted to determine nonspecific binding. As

TABLE 1. Characteristics of patients with severe TBI

Characteristic	Case 1	Case 2
Age	50	37
Sex	Male	Male
GCS score	3	4
CT findings	SDH	SAH
LOS	30	60
APOE status	$\epsilon 3/\epsilon 3$	$\epsilon 2/\epsilon 3$

LOS = length of hospital stay; SAH = subarachnoid hematoma; SDH = subdural hematoma.

FIG. 2. Florbetapir F18 PET images. Transverse sections of florbetapir F18 PET scans obtained in healthy age-matched controls (A, 50-year-old control for Case 1; B, 38-year-old control for Case 2); the patient in Case 1 at 1, 12, and 24 months after injury (D, E, and F, respectively); and the patient in Case 2 at 1, 12, and 24 months after injury (G, H, and I, respectively). Panel C is a positive control for cortical uptake of florbetapir F18. Figure is available in color online only.

determined previously in healthy controls who underwent serial scanning performed by our research group and others,²⁴ a change in SUVRs greater than 8% per year was deemed to be a meaningful increase. All aspects of the study described herein were approved by the institutional review board at the University of Texas Southwestern Medical Center (Dallas, Texas) prior to the initiation of any study-specific procedures.

APOE Genotyping

To test for apolipoprotein E (*APOE*) status, venous blood samples (8 ml) were collected into EDTA tubes, aliquoted into 1-ml tubes, and immediately frozen at -80°C . Genomic DNA was isolated by standard protocols. Genotypes were determined by Taqman assays (Applied Biosystems, Inc.).

Results

Prior to the scanning procedures, the Mini-Mental State Examination (MMSE), the Disability Rating Scale (DRS), and the Rivermead Post-Concussion Symptom Questionnaire¹³ were administered. The patient had a moderate-to-severe cognitive impairment, as indicated by an MMSE score of 19 at the 1-month time point. He

also had a moderately severe disability (DRS score of 9). Scores of 29 and 4 for the MMSE and DRS (moderate), respectively, indicated improved cognition and function at the 12-month time point. Also, the patient had a lower good recovery as indicated by a Glasgow Outcome Scale-Extended (GOS-E) score of 7 at Year 1. In contrast, at the 24-month time point, a worsening of both cognition (MMSE score of 22) and function (DRS score of 7) was observed (Table 2). At 1 month after injury, the patient displayed severe symptoms, which improved slightly at the 12- (moderate) and 24- (moderate) month time points (Table 3). He suffered from headaches, nausea, balance, dizziness, fatigue, and memory problems (Table 3). The results of *APOE* genotyping showed that the patient's status was *APOE* $\epsilon 3/\epsilon 3$. Comparison of the patient's florbetapir F18 PET scans from all imaging time points to scans obtained in a healthy age-matched control did not show any gross accumulation of amyloid within the cortical gray matter (Fig. 2), and thus analysis of amyloid levels within specific brain regions was performed. SUVR values from the 12 brain regions are listed in Table 4. In the patient in Case 1, comparison of region-specific SUVRs at 1 month with the 12-month scan only showed a decrease in amyloid in the hippocampus and caudate nucleus regions. Within the

TABLE 2. Outcomes of severe TBI

Outcome	Case 1	Case 2
MMSE		
1 mo	19	23
12 mos	29	29
24 mos	22	29
GOS-E		
12 mos	7	6
24 mos	7	7
DRS		
1 mo	9	15
12 mos	4	9
24 mos	7	5

hippocampus, 16% and 12% decreases in amyloid were observed in the left and right hippocampus, respectively, at Year 1. A similar finding was observed in the left (–18%) and right (–18%) caudate nucleus. A decrease in SUVR at the 12-month time point signifies amyloid clearance from the brain since the initial scan. In the caudate nucleus and left hippocampal brain regions, no change in amyloid deposition was observed at the 24-month time point. In contrast, a 15% increase of amyloid was found in the right hippocampus at the 24-month time point compared with the SUVR values collected at 12 months (Table 4, Fig. 3). With respect to post-TBI symptoms, worsening in memory problems (Rivermead symptom questionnaire) and cognitive outcomes (MMSE) was also observed at the 24-month time point compared with results obtained at 12 months (Tables 2 and 3).

Case 2

History

This 37-year-old man was involved in a motor vehicle collision and was admitted to Parkland Hospital with a severe TBI (GCS score of 4). A 1- to 2-mm midline shift and subarachnoid hemorrhage in the right frontotemporo-parietal cortex were identified by CT. A hemispherectomy was performed to reduce intracranial pressure in the right hemisphere. This patient also suffered a right hemispheric

TABLE 3. Rivermead symptom scoring for the patient in Case 1 at 1, 12, and 24 months after TBI*

Symptom	1 Mo	12 Mos	24 Mos
Headaches	4	4	3
Nausea &/or vomiting	3	2	1
Feelings of dizziness	4	3	2
Fatigue, tiring more easily	4	3	3
Forgetfulness, poor memory	4	2	4
Average symptom score	3.8 (severe)	2.8 (moderate)	2.6 (moderate)

* Symptom rating: no problem, 0–1.5; mild, 1.6–2.5; moderate, 2.6–3.5; severe, 3.6–4.

TABLE 4. SUVRs for 1, 12, and 24 months after TBI in Case 1*

Brain Region	1 Mo	12 Mos	24 Mos
Cingulate gyrus			
Anterior cingulate gyrus	1.17	1.07	1.19
Posterior cingulate gyrus	1.18	1.27	1.30
Dorsolateral prefrontal cortex	1.18	1.08	1.14
Frontal cortex	1.14	1.04	1.09
Hippocampus			
Left hippocampus	0.99	0.84 (–16%)	0.84
Right hippocampus	1.07	0.96 (–12%)	1.10 (+15%)
Anterior putamen			
Left anterior putamen	1.21	1.31	1.38
Right anterior putamen	1.32	1.28	1.31
Caudate nucleus			
Left caudate nucleus	0.94	0.81 (–18%)	0.86
Right caudate nucleus	0.96	0.83 (–18%)	0.84
Thalamus			
Left thalamus	1.29	1.21	1.15
Right thalamus	1.19	1.14	1.17
Occipital cortex	1.11	1.09	1.08
Orbital frontal cortex	1.08	0.97	0.96
Parietal cortex	1.30	1.22	1.29
Precuneus	1.22	1.22	1.29
Temporal cortex	1.23	1.17	1.21

* The values in bold within the 1-, 12-, and 24-month columns are higher than expected (5%–8% increase per year) when compared to the previous time point.

ischemic stroke during his hospital stay (Fig. 1C and D). He subsequently underwent 1.5 years of rehabilitation to improve swallowing, walking, and other motor abilities.

Serial Florbetapir F18 PET Imaging

Scanning was performed at 1, 12, and 24 months after TBI using the Siemens ECAT HR PET scanner. At each time point, the patient was injected with the florbetapir F18 tracer and a brain scan was conducted. Images were processed as described in Case 1, and 12 brain regions were surveyed to collect SUVRs to ascertain if changes in amyloid deposition occurred in a particular brain region.

APOE Genotyping

As in Case 1, venous blood samples (8 ml) were collected into EDTA tubes, aliquoted into 1 ml tubes, and immediately frozen at –80°C. Genomic DNA was isolated by standard protocols. Genotypes were determined by Taqman assays.

Results

At the initial scan (~ 1 month after injury), the patient had a DRS rating of 15 (severe disability), an MMSE score of 23 (moderate cognitive deficit), and Rivermead symptom scores indicating severe symptoms. At the later time points, the DRS score improved to 9 and 5 at the 12- and 24-month time points, respectively. The MMSE score improved to 29 at both 12 and 24 months. At Year 1, the

FIG. 3. Case 1: percent change of SUVR at 12 and 24 months after injury. Of the 12 brain regions surveyed, differences were observed in the left and right hippocampus (LHC, RHC) and caudate (LCD, RCD) brain regions.

patient had an upper moderate disability and Rivermead symptom scoring indicated severe symptoms. Improvement of symptom scoring to moderate and GOS-E scoring to low-good recovery was observed at 24 months. The symptoms reported for this patient were headaches, nausea, vomiting, balance, dizziness, fatigue, irritability, sadness, and memory problems (Table 5). Compared with the age-matched control, no evidence of a global increase of florbetapir F18 was found within the cortical tissue at the 1-, 12-, or 24-month time points (Fig. 2G–I). Due to the infarct area in the right hemisphere and possible data reliability issues, we only focused on the SUVR values from brain regions outside of the affected area. In the left hemisphere, compared with the 1-month scan, we observed an increase in amyloid at 12 months in the left anterior putamen (+11%) and a decrease in the left caudate nucleus (–48%), occipital cortex (–21%), and precuneus (–19%) brain regions. No increase in brain amyloid was observed at 24 months in any of the regions that were surveyed. Within the left anterior putamen (–12%), occipital cortex (–15%), and precuneus (–11%), compared with 12 months, a decrease in amyloid was measured at 24 months after TBI (Table 6, Fig. 4). The *APOE* genotype for this patient was *APOE* $\epsilon 2/\epsilon 3$.

TABLE 5. Rivermead symptom scoring for the patient in Case 2 at 1, 12, and 24 months after TBI*

Symptom	1 Mo	12 Mos	24 Mos
Headaches	4	4	3
Nausea &/or vomiting	4	4	2
Feelings of dizziness	4	4	3
Fatigue, tiring more easily	4	4	4
Feeling frustrated or impatient	3	3	2
Forgetfulness, poor memory	4	3	2
Average symptom score	3.8 (severe)	3.7 (severe)	2.6 (moderate)

* Symptom rating: no problem, 0–1.5; mild, 1.6–2.5; moderate, 2.6–3.5; severe, 3.6–4.

Discussion

In this study, we demonstrate the feasibility of obtaining serial scans in people who have survived a severe TBI event. Also, we show that in our sample of 2 TBI patients, brain scans obtained in the patient with the poorer outcome showed more amyloid accumulation than scans obtained in the patient with the better outcome or in healthy controls. The novelty of this study is in its conduct of se-

TABLE 6. SUVRs for 1, 12, and 24 Months after TBI: Case 2*

Brain Region	1 Mo	12 Mos	24 Mos
Cingulate gyrus			
Anterior cingulate gyrus	1.15	1.06	1.09
Posterior cingulate gyrus	1.14	1.16	1.05
Dorsolateral prefrontal cortex	0.92	0.97	0.91
Frontal cortex	0.94	0.90	0.86
Hippocampus			
Left hippocampus	1.01	1.03	1.12
Right hippocampus	0.75	0.23	0.23
Anterior putamen			
Left anterior putamen	1.08	1.23 (+11%)	1.09 (–12%)
Right anterior putamen	0.91	1.39	1.37
Caudate nucleus			
Left caudate nucleus	0.76	0.37 (–48%)	0.32
Right caudate nucleus	0.74	0.74	0.71
Thalamus			
Left thalamus	0.97	0.88	0.85
Right thalamus	1.31	0.78	0.54
Occipital cortex	0.79	0.62 (–21%)	0.53 (–15%)
Orbital frontal cortex	0.96	1.08	1.06
Parietal cortex	0.82	0.81	0.71
Precuneus	1.01	0.82 (–19%)	0.73 (–11%)
Temporal cortex	0.94	0.91	0.81

* Bolded brain regions from the right hemisphere were not included in subsequent analysis due to an infarct in the right hemisphere. The values in bold within the 1-, 12-, and 24-month columns are higher than expected (5%–8% increase per year) when compared to the previous time point.

FIG. 4. Case 2: percent change of SUVR at 12 and 24 months after injury. There were distinct changes in the 12- and 24-month SUVRs in the left anterior putamen (LANTPT), left caudate (LCD), precuneus, and occipital cortex brain regions compared with the 1-month time point.

rial scanning to compare the subacute (~ 30 days after TBI) amyloid levels to levels demonstrated by subsequent scans performed at 12 and 24 months after injury to determine the rate of change of amyloid in the brain within each person. By conducting serial scans, we can elucidate whether increases in amyloid deposition predict worsening of amyloid accumulation and/or neurodegeneration. Also, this methodology sheds light on the dynamics of amyloid deposition rates and patterns during the acute and chronic phases of TBI. Use of florbetapir F18, which has a substantial half-life (90 minutes), was instrumental in identifying both clearance and accumulation of amyloid at 12 and 24 months after injury when compared with SUVRs collected during the initial scan (~ 1 month after injury) within each subject. When surveying specific brain regions, we found that both of the patients experienced increases in brain amyloid after TBI (Figs. 3 and 4). Originally, we hypothesized that accumulation of amyloid in TBI survivors only occurs in individuals with poor outcomes. In contrast, as defined by the participants' DRS and GOS-E scores, we found that TBI patients with both moderate-to-severe and moderate-to-good outcomes exhibited increases in amyloid deposition in the brain. A main difference that we observed is that the patient with a moderate-to-good outcome (Case 1) exhibited a lower SUVR percent change (mean 15%) than the patient in Case 2, who experienced a moderate-to-poor outcome and a mean change of amyloid of about 26% at the 12-month time point. These differences may be related to the initial severity of their injuries.

To determine region-specific changes, we decided to compare the SUVRs between the 3 time points to determine if fluctuations exist throughout cortical and subcortical structures. This approach proved to be valuable in comparing the changes in brain amyloid within these serial scans. As shown in Tables 4 and 6, only a small number of brain regions were affected within each individual. Use of florbetapir F18 as a clinical marker for brain regions with heightened amyloid load may prove useful in predicting the onset of long-term cognitive and mood disorders. For example, the patient in Case 1 had an initial increase in amyloid in the left and right hippocampi that was reduced by 12 months after TBI. In contrast to the 12-month scan,

the 24-month scan showed a greater elevation of amyloid in the right hippocampus. This change may be directly related to the onset of severe memory problems, which was reported at the 24-month appointment by the patient in Case 1 and his family. Comparison of the SUVR values from multiple time points within a single patient may yield more reliable data on the timing of amyloid deposition after TBI. If the individuals who may be prone to accumulate amyloid can be identified, anti-amyloid therapies that become available in the future may provide an ideal treatment to reduce amyloid-related chronic secondary brain injury.

In previous studies, the likelihood of amyloid plaque deposition was more evident in TBI patients with Apo-E4 expression (50% in Apo-E4-expressing patients vs 30% in the non-Apo-E4-expressing group). The Apo-E4-expressing individuals also performed worse on cognitive tests at longer periods of time after injury.^{2,4,5,9,14,19,21,22,28,33,34} Given the increased risk for AD noted in Apo-E4-expressing patients, the increased likelihood for amyloid plaque deposition in *APOE* $\epsilon 4$ carriers with TBI supports the reported link between severe TBI and AD.^{4,7,9,14,19,22,25,27,28,31–34} Initially, we hypothesized that only Apo-E4 expressers would accumulate amyloid in the brain after TBI. Unfortunately, due to our limited sample size, we were unable to test our hypothesis. In our 2 cases, the patients' *APOE* genotypes were as follows: *APOE* $\epsilon 3/\epsilon 3$ in Case 1 and *APOE* $\epsilon 2/\epsilon 3$ in Case 2 (Table 1).

There are several recognized limitations of this study. Primarily, the limited sample size, lack of controls (trauma without TBI), variability of the injuries, and diverse pattern of amyloid accumulation between the participants limit the conclusions that can be drawn. However, the primary purpose of this study was to assess a serial imaging methodology. Using purposive sampling, we enrolled TBI patients who had improvements in neurological outcomes and were most likely to survive and participate in follow-up procedures, since the severe TBI population suffers from high morbidity and low follow-up. As a future direction, we plan to enroll TBI patients with both poor and good outcomes to determine if amyloid deposition rates differ between individuals with good outcomes and those

with poor outcomes. With respect to the diversity of amyloid deposition in the brain, the difference observed here may be due to the mode and location of the injury, which is highly variable within the TBI population. We also recognize that administration of an extensive neuropsychological battery would prove useful to determine relationships between amyloid deposition and cognitive/mood deficits. In addition to neuropsychological testing, in future definitive studies, we will also conduct diffusion tensor imaging and functional connectivity MRI to measure the integrity of the white matter within these populations.

In conclusion, this research sheds light on the use of florbetapir F18 PET imaging as a method to detect/monitor amyloid accumulation in the brain of TBI survivors. We found that within a 2-year period after severe TBI, amyloid accumulates at both early and late postinjury time points. By conducting follow-up scans, we were able to identify specific brain regions where amyloid accumulated after TBI as potential biomarkers for cognitive and/or mood deficits. As a future direction, administration of a thorough neuropsychological battery and MRI may prove useful in determining how amyloid deposition in certain brain structures correlates with cognitive performance and structural abnormalities after TBI at both the early and late time points within each individual.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Gatson, Mathews, Diaz-Arrastia, Minei. Acquisition of data: Gatson, Stebbins, Mathews. Analysis and interpretation of data: Gatson, Harris, Madden, Diaz-Arrastia. Drafting the article: Gatson, Diaz-Arrastia, Minei. Critically revising the article: Gatson, Mathews, Madden, Batjer, Diaz-Arrastia, Minei. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Gatson. Administrative/technical/material support: Stebbins, Mathews. Study supervision: Gatson, Mathews, Madden, Batjer, Minei.

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