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# A Pilot Study to Determine the Effectiveness of Bioelectrical Impedance Analysis as a Clinical Assessment Tool of Nutrition Status in Glioblastoma Multiforme Patients (The BEAM Study [BIA Effectiveness as Assessment Tool for GBM Patients])

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# A PILOT STUDY TO DETERMINE THE EFFECTIVENESS OF BIOELECTRICAL IMPEDANCE ANALYSIS AS A CLINICAL ASSESSMENT TOOL OF NUTRITION STATUS IN GLIOBLASTOMA MULTIFORME PATIENTS

(THE BEAM STUDY [BIA EFFECTIVENESS AS ASSESSMENT TOOL FOR GBM PATIENTS])

by

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CLINICAL NUTRITION

ABSTRACT

Glioblastoma multiforme (GBM) is a rare brain tumor, yet accounts for 80% of malignant brain tumors and has a five-year survival rate of < 5%. Few studies have evaluated nutrition recommendations and outcomes of this disease, including caloric needs. The purpose of this study was to find the best predictive equation for resting energy expenditure (REE) for GBM patients and evaluate bioelectrical impedance analysis (BIA) as a clinical tool for estimating REE and fat free mass (FFM) of GBM patients. REE was measured with indirect calorimetry. FFM was measured with DXA and estimated with BIA. Published predictive equations for REE were calculated to compare to measured REE. Six equations used variables easily attained in a clinical setting and three used FFM. Correlation analysis was used to evaluate the strength of the relationships between measured and predicted REE. Agreement between methods on the group level was assessed by comparing the group means of measured and predicted REE with paired t-tests. The Bland-Altman approach was used to find agreement between the methods on the individual level. Analysis included fifteen newly diagnosed GBM patients (7 male and 8 female; mean age 57.1±11.6 years) to evaluate equations using clinical variables and a subsample of eight to evaluate predictive equations using FFM. All the predictive equations overestimated measured REE. The Mifflin-St Jeor was the

only equation using clinical variables which was not significantly different from measured REE ($p=0.054$) and had the lowest bias (73 kcal/day) and narrowest limits of agreement. Likewise, Cunningham and Wang equations using FFM from DXA were not significantly different from measured ($p=0.261$ and $p=0.072$, respectively). BIA overestimated FFM compared to DXA, 54.1 kg and 49.2 kg, respectively ($p<0.001$). More visits with both DXA and BIA measurements available are needed before predictive equations with clinical variables and predictive equations with FFM can be compared. Due to the ease of obtaining clinical variables and the low bias and narrow limits of agreement found for the Mifflin equation, at this time it appears to be the best predictive equation for individuals with GBM.

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| | |
|---|---|
| BEE | basal energy expenditure |
| BIA | bioelectrical impedance analysis |
| BMI | body mass index |
| BMR | basal metabolic rate |
| CRU | Clinical Research Unit |
| DXA | dual x-ray absorptiometry |
| FFM | fat free mass |
| FM | fat mass |
| ft | feet |
| GBM | glioblastoma multiforme |
| HB | Harris-Benedict equation |
| hrs | hours |
| IC | indirect calorimetry |
| IRB | Institutional Review Board |
| kcal | kilocalories |
| kcal/day | kilocalories per day |
| kcal/kg | kilocalories per kilogram |
| kg | kilogram |
| L | liter |
| lbs | pounds |
| m | meters |

| | |
|---|---|
| NIH | National Institutes of Health |
| REE | resting energy expenditure |
| RMR | resting metabolic rate |
| RQ | respiratory quotient |
| SD | standard deviation |
| TEE | total energy expenditure |
| UAB | University of Alabama at Birmingham |
| $VCO_2$ | volume carbon dioxide |
| $VO_2$ | volume oxygen |
| WHO | World Health Organization |
| wt | weight |

# INTRODUCTION

Glioblastoma multiforme (GBM) is a rare brain tumor, yet accounts for 80% of malignant brain tumors and has a five-year survival rate of less than 5%. New therapies are under investigation to increase life expectancy in this population. Little is known about the effect nutritional status has on this disease and its impact on life expectancy and quality of life. Similarly, the energy needs of GBM patients, especially during treatment, are unknown. Caloric needs in other cancer populations have been studied and predictive equations have been found to underestimate and overestimate actual needs.

A gap in our understanding of GBM treatment is the lack of information about caloric needs for GBM patients. The objective of this research project is to evaluate previously published predictive equations of resting energy expenditure (REE) to find the most suitable equation for the GBM population and evaluate bioelectrical impedance analysis (BIA) as a possible clinical nutrition assessment tool. The long term goal of this research is to provide GBM patients more individualized clinical care and personalized nutrition recommendations with the intent of giving them a sense of empowerment and control over their treatment.

## Hypothesis and Specific Aims

*Hypothesis 1*

An existing predictive equation can accurately predict REE of newly diagnosed GBM patients, at both the group and individual level.

*Specific Aims*

1. Measure baseline REE of GBM patients by indirect calorimetry (IC).
2. Calculate predicted REE from selected previously published and commonly used predictive equations (Harris Benedict, Harris Benedict with weight adjusted for obesity, Mifflin-St Jeor, Schofield, Owen, the ratio method [20kcal/kg], and the equation used by the Biodynamics 310 BIA software [available in only n=11 patients) in a sample of GBM patients.
3. Measure the strength of the relationship between REE and each predictive equation by correlation analysis.
4. Assess agreement between group mean of REE measured by IC and group mean of energy expenditure from each predictive equation by paired *t*-test.
5. Assess agreement between REE measured by IC and REE from each predictive equation by the Bland-Altman approach.

*Hypothesis 2*

BIA can estimate FFM and fat mass (FM) measured by DXA in a subsample of eight GBM patients.

*Specific Aims*

1. Measure FFM and FM of participants by full body DXA scans (n=4 DXA scans completed at baseline, n=4 DXA scans completed at 6-months).
2. Estimate FFM and FM by BIA at same visit DXA scan is completed.
3. Compare FFM estimated by BIA to FFM measured by DXA by paired *t*-tests.
4. Compare FM estimated by BIA to FM measured by DXA by paired *t*-tests.
5. Measure the strength of the relationship between FFM and FM from DXA and FFM and FM from BIA by correlation analysis.

*Hypothesis 3*

An existing predictive equation using FFM can accurately predict REE in a subset of eight GBM patients, at both the group and individual level.

*Specific Aims*

1. Calculate predicted REE from FFM determined by BIA using the Cunningham and Wang equations (at the same visit DXA was performed; n=4 DXA scans completed at baseline, n=4 DXA scans completed at 6-months).
2. Calculate predicted REE from FFM determined by DXA using the Cunningham and Wang equations (at a visit where BIA measurements are available).
3. Measure the strength of the relationship between REE and each predictive equation using FFM by correlation analysis.
4. Assess agreement between group mean of REE measured by IC (from same visit as DXA and BIA) and group mean of energy expenditure of each predictive

equation using FFM (Cunningham with DXA FFM, Cunningham with BIA FFM, Wang with DXA FFM, Wang with BIA FFM, and the equation used by the Biodynamics 310 BIA software) by paired *t*-test.

5. Assess agreement between REE measured by IC and REE from each predictive equation using FFM by the Bland-Altman approach.

# REVIEW OF LITERATURE

## Glioblastoma Multiforme

### *Prognosis and Treatment*

GBM is the most common tumor of neuroepithelial tissue and represents 49.8% of all tumors in this category diagnosed between 2004-2006 (1). In relation to other types of cancer and even other brain tumors, the incidence of GBM is uncommon. Despite its rarity, prevention and treatment of GBM is a significant concern because it accounts for 80% of malignant brain tumors and the five-year survival rate is less than 5% (1). Most patients die within two years of diagnosis despite aggressive treatment including surgical resection (degree dependent on tumor location (2)), steroid (typically dexamethasone) therapy to control intracranial pressure and the resulting symptoms (3), radiation therapy, and chemotherapy (4). New therapies to increase life expectancy in this population are under investigation, but little has been documented about the nutritional implications of this disease and their impact on life expectancy and quality of life.

### *Common Nutrition Concerns for GBM Patients*

It is not uncommon for GBM patients to experience weight loss or gain in the first months following diagnosis of GBM. Depending on how the patient deals with the stress of the recent diagnosis, either one can happen. Weight gain is often due to the standard steroid therapy prescribed to control inflammation. The steroid therapy can result in fluid

retention and hyperglycemia (5, 6). Short-term use of glucocorticoids do not significantly increase REE (5), but many GBM patients report increased appetite while on their steroid regimen.

### *Risk of GBM*

Obesity is linked to several types of cancer and often results in a poorer prognosis (7). Jones et al. (8) found body mass index (BMI) in newly diagnosed and previously untreated GBM patients was not related to survival time. BMI is an easy clinical assessment, but it cannot distinguish between fat and lean mass. Therefore, the influence adiposity or lean mass separately has on survival time cannot be determined. This suggests the importance of studying the association between other measures of body composition and prognosis (8). In a large multicenter European prospective cohort (EPIC) study of nutrition and lifestyle and cancer risk, Michaud et al. (9) found no associations between weight, waist circumference, waist-hip ratio, or BMI and risk of glioma or GBM.

## Bioelectrical Impedance Analysis

BIA is a quick, portable, and noninvasive tool to estimate body composition. A Bioelectrical Impedance Analyzer is an instrument that introduces an alternating electrical current into the body and measures the flow of electricity between the sites of electrodes (10). According to a statement released by the National Institutes of Health (NIH), this current is below the threshold of perception, and stimulation of electrically excitable tissues (i.e. nerves or cardiac muscles) is unlikely at this level (11). BIAs come

in a variety of forms, such as single frequency or multiply frequency, and differ in the path of the electrical current through the body, such as foot to foot, hand to hand, foot to hand. BIA can come as bipolar, tetrapolar, or eight-polar models.

BIA can estimate FFM, the sum of bone mineral mass and lean mass (12). Obtaining a good measurement by BIA is very sensitive to the participant's hydration status, recent food intake or strenuous activity, and electrode placement, among other factors (11). Since FFM from BIA can be used to estimate metabolic rate, it was necessary for us to have confidence an accurate FFM could be obtained. Several researchers have compared FFM from BIA to other more robust measurements of body composition, such as labeled water (13) and DXA (14). Piers et al. (13) found poor agreement in FFM when compared to labeled water. Steiner et al. (12) found BIA commonly underestimated FFM when compared to DXA, but Pateyjohns et al. (14) found single-frequency and multi-frequency BIA modes over predicted FFM compared to DXA. Both BIA modes had good relative agreement with FFM from DXA when the average of the sample was evaluated, but the limits of agreement were wide, indicating the accuracy of the estimate of FFM was decreased for an individual (14).

Barak et al. (15) developed predictive equations by sex in 40 hospitalized patients referred to nutrition support using FFM and FM from a single frequency BIA and age. In another 36 patients the accuracy of the equations was tested and compared to the REE predicted by the Harris Benedict (HB) equation. The new predictive equations accurately predicted REE and had significantly less measurement error when compared to HB (15). In conclusion, BIA is not the most ideal method to determine an accurate FFM or BMR, but due to its portability and ease of use, it is worth finding an appropriate predictive

equation for REE from FFM estimated by BIA since it could provide beneficial information to GBM patients.

## Energy Expenditure

### *Basal and Resting Energy Expenditure*

Age, sex, body size and composition, in particular fat-free mass (16), are the main influences on REE, also referred to as resting metabolic rate (RMR). REE is the energy used by an individual when fasted and at complete rest. Basal energy expenditure (BEE), or basal metabolic rate (BMR), is the minimum number of calories needed to maintain homeostasis and can be as much as 10-20% less than REE (17). The largest component of total energy expenditure (TEE) is BEE and accounts for up to 70% of the calories an individual uses in one day (17). Digestion and metabolism of food and level of activity increases energy expenditure and compose the remaining two components of TEE (17-19).

BEE is measured first thing after waking, following an overnight fast (17, 20) in a strict thermo-controlled environment to prevent shivering (20). A measurement of energy expenditure with any deviation from the parameters for BEE is usually referred as REE (17). A common way to measure energy expenditure for research purposes is by indirect calorimetry (IC). IC determines REE by measuring the amount of oxygen inhaled and the carbon dioxide exhaled in a closed environment (17) and interprets the volume of the gases into REE using the Weir formula (21). Benefits of IC are it does not require a long research visit like needed for a room calorimeter and the subject does not have to complete a 24 hour urine collection as needed for the doubly labeled water method. For

ease of reading and due to their many similarities, throughout the rest of this work BEE and REE will be used synonymously.

*The Effect of Cancer on REE*

Hyltander et al. (22) studied energy expenditure in 202 hospitalized patients with solid tumors (before chemotherapy or radiation) and non-cancer (control) patients. Each group contained individuals who were classified as either weight-losing (loss of >4% of normal body weight in the last six months) or weight-stable. They found that cancer patients had a significantly higher REE compared to the non-cancer controls, regardless of a weight loss or maintenance (weight-losing cancer vs. weight-losing controls and weight-stable cancer vs. weight-stable controls, both $p< 0.025$). The findings in this sample reached statistical significance, but the clinical significance is questionable because a significant change in REE is not seen in all cancer patients (22). An increase in REE in cancer patients is likely a result of disease progression and is postulated to be one of the factors contributing to cancer cachexia (23). Whether surgical removal of the tumor is curative or palliative can also have differing effects on REE postoperatively (24). Luketich et al. (24) found patients who received curative removal of tumors were more likely to return to a normometabolic state after surgery, regardless of preoperative metabolic state. On the other hand, palliative surgical removal of the tumor resulted in an increase in metabolic rate regardless of the preoperative metabolic state.

*Predictive Energy Expenditure Equations*

Variables used in predictive equations for REE range from those easily obtained in a clinical setting (age, sex, height, weight) to variables more complicated to measure or calculate (fat mass, fat free mass, body surface area, etc). Predicted REE is often multiplied by stress factors to account for the increase in metabolic rate due to the stress of the disease (25). One will see in the following select review of published predictive REE equations the study of caloric requirements in humans is not a new interest. Most of the classical studies were completed in healthy individuals, with males represented more frequently than females.

*Harris Benedict.* The HB equation was one of the first predictive energy expenditure equations developed using multiple regressions (26, 27). It remains one of the best known and most used predictive equation, but is not suggested for critical care patients (26) or many other populations (28). HB estimates BEE with a formula that uses weight, age, height, and sex (19). HB is criticized for not being an accurate predictive equation for the current Western population due to the inclusion of mostly normal weight individuals from almost a century ago (25, 29). HB overestimates the REE of overweight and obese individuals when actual weight is used (30, 31). For this reason, we also calculated HB with weight adjusted for obesity (18) (formula for adjusted weight in METHODOLOGY section). A similar study to this one showed Harris-Benedict x 1.3 overestimates REE in pancreatic cancer patients (32); therefore, we did not include it in our analysis. Table 1 shows the HB equations.

*Mifflin-St Jeor.* In 1990, Mifflin et al. (33) developed the predictive formulas commonly referred to as the Mifflin-St Jeor equations after studying the interactions between measured REE and weight, height, age, sex, FFM determined by skinfold measurements, percent ideal weight, BMI, and waist-to-hip ratio collected from 482 lean and obese men and women. Data from this study is thought to better represent a modern Western population because of the inclusion of more non-lean subjects (29). Percent FFM, age, height and weight were found to be highly correlated to REE in both men and women, but because accurate FFM from skin folds is highly dependent on well trained practitioners, Mifflin et al. (33) included easily gathered variables in their final equations. Table 1 shows the Mifflin-St Jeor equations by sex.

*Schofield.* In 1985, Schofield (34) published a meta-analysis on basal metabolism and attempted to eliminate studies with poor or inconsistent methodology to develop his own predictive equation from a combination of the data. The resulting dataset included males and females and crossed the lifespan. Correlations were broken down into age groups, similar to the clinical age groups (infant, child, adolescent, adult, older adult). From a clinical perspective, there is freedom in not depending on an accurate height (incorrect height reported by the patient, measurement error (25), etc). Table 1 shows the Schofield predictive equations per sex by age group.

*Owen.* In 1986, Owen et al. (35) published a study on the relationships they found between REE and age, anthropometrics, and body composition (FFM and FM) from skin folds and densitometry of 44 healthy lean and obese females between the ages of 18-65

years. Later in 1987, Owen et al. (36) published their findings from a similarly designed study of 60 lean and obese men, ages 18-82 years. As found by Mifflin et al. (33), FFM is well correlated with and a good predictor of REE. Both publications by Owen et al. (35, 36) concluded that since body weight was highly correlated with RMR and the most easily collected clinical parameter, it would be the most reasonable variable to use to develop a predictive equation. The Owen predictive equations for each sex are presented in Table 1.

*Ratio Method.* The ratio method is a common and quick way for clinicians to estimate total daily caloric needs based only on the disease or stress state (a higher factor is used for higher metabolic activity (25)) and weight (37). The maintenance level for total caloric intake for cancer patients is suggested to be 25-35 kcal/kg body weight (37). Since this estimates total calories needed, 20 kcal/kg was proposed to be equivalent to REE (32, 38). The ratio method used in this study is reported in Table 1.

*Predictive Equations from FFM: BIA, Cunningham and Wang.* Many investigators have found FFM is highly associated with REE (33, 35, 36, 39), but it is often difficult and rare for practitioners to have access to a patient's FFM in order to estimate caloric needs. A benefit of using FFM is age, sex, height, and weight is not needed because it takes into account the most metabolically active component of the body (40).

In 1991, Cunningham (29) combined published regression equations of REE from FFM in eight large studies ($n$ = 100+) of REE to form a mean equation. The influence of

each study on the final regression was weighted for its size. The eight selected studies included lean and obese men and women, and reported FFM explained 60-85% of the variation observed in REE. The new predictive equation from Cunningham's combination of the regressions is in Table 1.

Similarly, in 2000, Wang et al. (39) calculated a new predictive equation for REE from FFM using 15 published regressions. Lean and obese men and women were represented. Unlike Cunningham (29), Wang et al. (39) did not limit their inclusion to only large studies and did not weight the final equation based on the study size of the contributing formula. The Wang predictive equation is in Table 1.

**Table 1.** Selected predictive equations compared in a sample population of GBM patients.

| **Predictive Equation** | **Formula** |
|---|---|
| Harris Benedict (27), 1919 | Men: BEE (kcal/day) = 66.47 + 13.75 x wt + 5.0 x ht – 6.75 x A<br>Women: BEE (kcal/day) = 655.09 + 9.56 x wt + 1.84 x ht – 4.67 x A |
| Mifflin-St Jeor (33), 1990 | Men: REE (kcal/day) = 10 x wt + 6.25 x ht – 5 x A - 161<br>Women REE (kcal/day) = 10 x wt + 6.25 x ht – 5 x A + 5 |
| Schofield (34), 1985 | Men, 30-60 years: BMR (MJ/day) = (0.048 x wt) + 3.653<br>Men, >60 years: BMR (MJ/day) = (0.049 x wt) + 2.459<br>Women, 30-60 years: BMR (MJ/day) = (0.034 x wt) + 3.538<br>Women, >60 years: BMR (MJ/day) = (0.038 x wt) + 2.755 |
| Owen (35, 36), 1986 and 1987 | Men: RMR (kcal/day) = 10.2 x wt +879<br>Women: REE (kcal/day) = 7.18 x wt +795 |
| Ratio Method (37) | Both sexes: REE (kcal/day) = wt x 20 |
| BIA (10) | Both sexes: BMR (kcal/day) = 31.2 x FFM |
| Cunningham (29), 1991 | Both sexes: REE (kcal/day) = 21.6 x FFM + 370 |
| Wang (39), 2000 | Both sexes: REE (kcal/day) = 21.5 x FFM +407 |

wt: weight in kg, ht: height in cm, A: age in years, FFM: fat free mass in kg

*Predicting Energy Expenditure in Cancer Patients*

Over the last few decades, more attention has been paid to the metabolic rate of specific disease states, including cancer (16, 24, 32, 41). Achieving adequate caloric balance to restore nutrients lost or to meet increased needs during treatment is important for cancer patients (41). Some researchers suggest overfeeding can be as detrimental to the cancer patient as under nutrition because it can promote tumor progression (42). Therefore, it is important to find a predictive equation to best estimate a cancer patient's caloric needs.

Garcia-Peris et al. (41) compared REE determined by IC and BEE estimated by HB, and found HB underestimated REE in patients with head and neck cancers before and during chemotherapy and radiotherapy. Furthermore, an increase in REE still was observed at the conclusion of treatment, and HB could not predict the increase in caloric needs generated by the stress of recovering from chemotherapy and radiotherapy. This discrepancy is due in part to the weight loss experienced by the subjects (mean BMI dropped from 24.7 to 22.3) and the assumption of HB that weight greatly influences REE (41). Others have found treatment may not increase REE as much as observed by Garcia-Peris et al. (41) or as much as recommended by standard predictive equations for cancer patients (38).

Bauer et al. (32) compared eight predictive equations for REE to REE measured by IC in eight pancreatic cancer patients receiving palliative care; four participants had multiple measurements to bring the number of observations up to 15. Six of the predictive equations evaluated used easy to obtain variables such as height, weight, age and sex. The other two equations used FFM estimated by deuterium labeled water. Means

of the predicted and measured REE were compared using Student's t-test, and agreement between measured and predicted was determined by the Bland-Altman approach (43). The Wang and HB (without stress factor of x 1.3) equations were concluded to be the best for their sample of pancreatic cancer patients, due to low bias and narrowest limits of agreement (32).

The accuracy of predictive equations for REE in cancer patients is mixed. Some investigators have found HB, one of the most commonly used equations in the United States (44), to be a good predictor (32, 38) while others have not (41). To the knowledge of the investigators, little is currently known about REE in brain tumor patients, especially GBM, or the most appropriate way to estimate REE in this population when IC is not available. Five of the equations assessed by Bauer et al. (32) were included in this study to be evaluated in a sample population of newly diagnosed GBM patients.

# METHODOLOGY

## Subjects and Recruitment

The data for this project were collected as part of "A Pilot Study to Determine the Effectiveness of Bioelectrical Impedance Analysis as a Clinical Assessment Tool of Nutrition Status in Glioblastoma Multiforme Patients (**The BEAM Study** [BIA Effectiveness as Assessment Tool for GBM Patients])" (Clinical Research Unit (CRU) protocol # 2099). The UAB Institutional Review Board (IRB protocol # F110128003) and UAB Comprehensive Cancer Center (CTRC # UAB 1106) approved this study. The full BEAM study is designed as a case-control study to observe changes in resting energy expenditure and nutrition status through one year of treatment for GBM.

Men and women with newly diagnosed GBM were recruited from the outpatient Neuro-oncology Clinic at University of Alabama at Birmingham (UAB) Kirklin Clinic. Eligible individuals were identified to the study coordinator as meeting the inclusion criteria of GBM by the doctors or nurse practitioners of the Neuro-oncology Clinic after histological confirmation of GBM (WHO grade IV astrocytoma). Age- (+/- 2 years), sex, BMI category- (underweight, normal weight, overweight, and obese), and race-matched controls were also recruited and enrolled, but their data will not be presented in this project. Goal enrollment was 20 cases with newly diagnosed GBM, enrolled within six weeks of diagnosis. Participants were required to be at least 19 years of age, and women of childbearing potential were required to have a negative pregnancy test before

participating in this study. Four conditions which would contradict the safety and accuracy of BIA and/or the DXA measurements were exclusion criteria: implanted pacemakers or defibrillators, pregnancy, chronic edema, and/or an amputated extremity.

Informed consent was obtained from all participants after full explanation of study protocol, the procedures, and potential risk of involvement. Data from 15 participants with GBM were used for this project.

## Protocol

Participants presented to the UAB CRU in the morning after an overnight fast (10-12 hours). Subjects were consented at or before the first visit. If needed, a urine pregnancy test was complete on women of childbearing potential. The subject's height, weight, REE, and body composition were collected. A description of the visit (baseline and 6-month) follows.

## Body Composition

### *Anthropometric Measurements*

Body weight was measured in pounds to the closest 0.1 lbs by a digital scale (Scale-Tronix Model 6702, Wheaton, IL, USA) in light street clothing and no shoes. Height was measured at the first visit by a wall-mounted, digital stadiometer (Digi-Kit, Measurements Concepts & Quick Medical, North Bend, WA, USA) or was pulled from the electronic medical chart. Height was recorded in inches to the nearest 0.01 inch. Body mass index (BMI; $kg/m^2$) was calculated using the National Heart Lung and Blood Institute's online BMI calculator (http://www.nhlbisupport.com/bmi/).

*Bioelectrical Impedance Measurements*

Bioelectrical impedance analysis was performed with Biodynamics Body Composition Analyzer Model 310e (Seattle, Washington, USA) to estimate body composition (FM and FFM in pounds) and BMR (kcal/day). Two separate BIA measurements were collected separated by ~1 hour. The first BIA was before IC and the second BIA was run after the IC was completed. The average of the two measurements for BMR, FFM and FM was used. All analyses were conducted by Rebecca Barnhill to prevent inter-technician differences.

Participants were instructed not to consume alcohol for 24 hrs before BIA test and abstain from strenuous exercise at least 4 hrs before. Participants were also asked to drink caffeine- and calorie-free beverages before the study visit to replenish fluids after the overnight fast. Water was provided for the participant during the study at his or her request. The participant rested in the supine position for 15 minutes (11). Sites on the dorsum of the right hand and wrist, and dorsum of the right foot and ankle were prepped with an alcohol prep wipe. Electrodes were placed at the four locations, and the leads were attached with the red above the black. The participant's age, height, and body weight was entered into the analyzer. The participant was instructed to lie still with arms not touching the trunk and legs slightly apart as to not touch, and relax while the BIA ran. The BIA returns its analysis in approximately 20 seconds. The time needed to conduct the BIA is approximately 20 minutes.

*Dual X-ray Absorptiometry*

Full body DXA scans were completed by the Osteoporosis Clinic at the UAB Kirklin Clinic by one of two certified technologists on a Hologic Discovery W DXA scanner (Hologic Inc., Bedford, MA, USA). The software calculated FM and FFM in grams, which was converted to pounds for comparison of FFM and FM from BIA. Subjects were scanned in hospital gowns and in the supine position with arms placed at their sides. Additional phantom scans beyond what was completed for machine maintenance was not required for this study. Eight participants completed the DXA scan at the baseline visit and four at the 6-month visit. Four of the eight baseline visits were missing BIA measurements, so they were excluded. Only the four baseline visits and the four 6-month visits with both a DXA and BIA were included in statistical analysis comparing DXA and BIA.

## Resting Energy Expenditure

*Measurement of REE*

Resting Energy Expenditure (REE) was determined by canopy indirect calorimetry (IC) (Vmax Encore 29, Yorba Linda, CA, USA) at baseline and for four subjects at 6-months. Due to the requirement of an overnight fast, a standard meal was provided to the participant after completion of IC. The participant was instructed to lie supine for a 30 minute rest period before the measurement. Before each measurement, gas analysis was performed with two gas tanks with known gas compositions, and the mass flow sensor was calibrated with a 3 L syringe, per manufactures instructions. After the subject's age, height, and weight were entered into the software, the clear plastic

canopy was placed over the participant's head and shoulders to collect and measure the expired air. A minimum of 30 minutes of data was collected. The first five minutes were deleted to account for the participant acclimating to breathing under the canopy. Steady state regions were determined by the computer software as a variation of $VO_2$ and $VCO_2$ less than 10%, and RQ less than 5% for a five minute period. Data points were then manually selected to determine REE. The IC software determines the calories used by the participant with the de Weir calculation (21).

**Table 2.** Procedures completed at baseline and 6-month study visits.

| Baseline | 6-month |
|---|---|
| -Signed informed consent process | -Urine pregnancy, if needed |
| -Urine pregnancy, if needed | -Weight |
| -Height and weight | -BIA |
| -BIA | -REE by IC |
| -REE by IC | -DXA scan (*n*=4) |
| -DXA scan (*n*=4) | |

*Calculation of Predictive Equations*

The previously described formulas by HB, HB using adjusted weight for obese individuals, Mifflin, Schofield, Owen, and the Ratio method were calculated using the subject's age, current weight, and height collected at the study visit. FFM (converted to kg) from the DXA and BIA were entered into the Cunningham and Wang formulas. All results were converted to the same units (kcal/day) before comparison. BMR from BIA was calculated by the manufacturer's software. Adjusted weight was calculated and used in the second calculation of the HB equation for obese individuals (BMI ≥30) (18).

Adjusted weight was calculated by the following formula:

Adjust wt = 0.5(actual wt – ideal wt*) + ideal wt*

*Ideal wt for women: 100 lbs for first 5ft and 5 lbs for each additional inch

men: 106 lbs for first 5ft and 6 lbs for each additional inch

## Statistical Analysis

The descriptive variables of the study sample are presented as means±standard deviations (SD) and frequencies. Paired t-tests were used to determine the differences between each predicted REE and measured REE. The Bland Altman approach (32, 43, 45) was used to assess the agreement between measured REE and predicted REE. This method calculates bias (the mean of the differences between the predicted and measured REE) and the limits of agreement (±2 SD from the mean difference). The number of data points outside the limits of agreement on each Bland Altman plot are noted in Tables 3 and 5. Pearson's correlation analysis was completed to examine the associations between REE from each predictive equation and measured REE. Statistics dealing with information from DXA include eight subjects because both DXA scans and BIA measurements were only available for these individuals. Statistical significance was achieved at $P<0.05$ (two-tailed). Statistical analysis was completed on SAS for Windows (Version 9.2, SAS Institute Inc., Cary, NC).

# RESULTS

In the data for this project, men and women were equally represented (n=7, 46.7% and n=8, 53.3%, respectively). All subjects were Caucasian and ranged in age from 35-73 years old, with the mean age 57.1±11.6 years. Four subjects were normal weight (26.7%), nine were overweight (60.0%), and two were obese (13.3%). The median number of days between diagnosis and completion of the first study visit was 30 days (mean 28.7±11.6 days). This is noteworthy because GBM patients typically are diagnosed after surgical removal of the tumor (as much as is feasibly possible), and this shows they would have time to heal from surgery before completing the first study visit. At the time of the first study visit, only two patients had started standard concurrent chemoradiation treatment and both were less than one week into their treatment.

As a primer to the rest of the results, correlations between measured and predicted are expected to exist and be significant because predicted equations for REE were developed based on this principle. On the other hand, the paired t-tests should show the predicted REE is not significantly different from measured REE, i.e. predicted and measured are the same.

Mean measured REE was 1395±221 kcal/day. The minimum and maximum measured REE was 1096 kcal/day and 1962 kcal/day, respectively. Table 3 shows the mean REE±SD, bias, and limits of agreement for the predictive equations using easily obtained clinical variables and BMR from BIA. These results address the first hypothesis

that a previously published predictive equation can accurately predict REE of GBM patients.

**Table 3.** Predicted resting energy expenditure (REE) from equations using easily measured clinical variables and the BIA software

| Equation | Predicted REE (Mean±SD; kcal/day) | Bias (kcal/ day) | Limits of agreement (±2 SD; kcal/day) | Points outside B-A plot | Paired t-test* | | Correlation** | |
|---|---|---|---|---|---|---|---|---|
| | | | | | t value | P value | r value | P value |
| Harris Benedict | 1527±188 | 132 | 268 | 1 (6.7%) | 3.80[b] | 0.002 | 0.797 | <0.001 |
| Harris Benedict adjusted wt[a] | 1503±179 | 108 | 239 | 2 (13.3%) | 3.50[b] | 0.004 | 0.842 | <0.001 |
| Mifflin-St Jeor | 1468±185 | 73 | 269 | 1 (6.7%) | 2.10[b] | 0.054 | 0.795 | <0.001 |
| Schofield | 1536±193 | 141 | 295 | 0 (0.0%) | 3.69[b] | 0.002 | 0.754 | 0.001 |
| Owen *et al.* | 1502±215 | 106 | 334 | 1 (6.7%) | 2.47[b] | 0.027 | 0.707 | 0.003 |
| Ratio Method | 1545±197 | 150 | 409 | 3 (20%) | 2.84[b] | 0.013 | 0.528 | 0.043 |
| BIA | 1637±305 | 223 | 344 | 1 (9.1%) | 4.29[c] | 0.002 | 0.825 | 0.002 |

SD: standard deviation
B-A plot: Bland Altman plot
*Comparison between predicted and measured REE
**Correlation between predicted and measured REE
[a] wt: weight entered in HB adjusted for obesity, Adjusted wt = 0.5(actual wt – ideal wt) + ideal wt with ideal wt calculated as follows for women: 100 lbs for first 5ft and 5 lbs for each additional inch; and for men: 106 lbs for first 5ft and 6 lbs for each additional inch
[b] Evaluated on 15 subjects (14 degrees of freedom)
[c] Only 11 observations available (10 degrees of freedom): BIA not available for 4 subjects

All predictive equations using clinical variables were statistically correlated with measured REE. However, this only shows strength of the relationship between predicted and measured REE, and not agreement between the methods. There were statistically significant differences between the means of all the predicted REE and the mean measured REE, except for the Mifflin-St Jeor equation ($p = 0.054$). Bias was calculated as the mean of the individual differences between the predicted and measured REE. All the predictive formulas had the tendency to overestimate actual REE. The Mifflin-St Jeor equation had the lowest observed bias; on average Mifflin-St Jeor overestimated REE by

73 kcal/day and was able to predict the REE within the limits of agreement in 93.3% of the sample. The next two predictive equations with the lowest bias were the Owen equation (106 kcal) and HB equation with adjusted weight (108 kcal), but the mean predicted REE was significantly different than the mean measured REE.

The two equations with the greatest bias also had the widest limits of agreement. The predictive equation used by the BIA software had the highest bias (223 kcal/day) and the ratio method had the second highest (150 kcal/day). The limits of agreement ranged from the narrowest for the HB with adjusted weight (239 kcal/day) to the widest for the ratio method (409 kcal/day) and BIA software (344 kcal/day). With the exception of the Schofield equations, all the equations had points outside their Bland Altman plot, indicating an individual's predicted REE was outside the limits of agreement (±2SD of the bias) of that particular predictive equation.

Interesting, though not statistically significant, differences were found between the HB equation and the HB equation using adjusted weight. By using adjusted weight for the two obese subjects in the second calculation of the HB equation, bias reduced from 132 kcal to 108 kcal, the limits of agreement were reduced, and the correlation with measured REE slightly increased ($r=0.797$ to $r=0.842$). The means of measured REE and predicted REE by HB with adjusted weight remained statistically different ($p = 0.004$). HB without adjusted weight had the fourth lowest bias (132 kcal/day), or average of the differences between measured and predicted.

Table 4 presents the data for the second hypothesis and shows the comparisons of body composition by BIA and DXA in eight GBM participants who had DXA and BIA measurements available at the same visit. FFM and FM from both methods were highly

correlated with each other, as shown in Table 4. Despite the strength between the relationships, BIA overestimated the mean FFM when compared to DXA (54.1kg and 49.2 kg, respectively). This overestimation was statistically significant (P<0.001). On the other hand, BIA significantly underestimated (p= 0.007) FM when compared to DXA (26.0 kg and 29.2 kg, respectively).

**Table 4.** Weight of FFM and FM collected in 8 GBM patients by BIA and DXA

| Body Compartment and Measurement Method | Weight (Mean±SD; kg) [Range] | Paired t-test* | | Correlation** | |
|---|---|---|---|---|---|
| | | t value | P value | r value | P value |
| FFM from BIA | 54.1±10.0 [44.7-71.1] | 5.49[a] | <0.001 | 0.971 | <0.001 |
| FFM from DXA | 49.2±9.1 [40.8-64.8] | | | | |
| FM from BIA | 26.0±5.4 [17.3-33.9] | -3.79[a] | 0.007 | 0.893 | 0.003 |
| FM from DXA | 29.2±5.1 [21.7-35.7] | | | | |

SD: standard deviation
FFM: fat free mass
FM: fat mass
*Comparison between masses measured by BIA and DXA
**Correlation between masses measured by BIA and DXA
[a] 7 degrees of freedom

Table 5 presents the data for the third hypothesis and the comparisons between measured REE and REE predicted using FFM from BIA or DXA. These results are from the same subsample of eight participants with both DXA and BIA available at the same visit. All the predictive equations using FFM were correlated with measured REE. As with the equations using the clinical variables, all the predictive equations overestimated measured REE, and again the equation programmed into the BIA overestimated REE the greatest (255 kcal). There was no significant difference between the mean measured REE (1390±208 kcal/day) and the means predicted by the Cunningham (1433±196 kcal/day)

and Wang (1466±195 kcal/day) equations with FFM from DXA. These two methods also had the lowest bias, 44 kcal and 76 kcal respectively, and narrowest limits of agreement of all five predictive methods evaluated. The equation used by the BIA software had the greatest bias and widest limits of agreement. None of the equations predicting REE with FFM had points outside their Bland Altman plot, signifying all data plotted within the limits of agreement.

**Table 5.** Predicted resting energy expenditure (REE) from equations using FFM from DXA or BIA

| Equation | Predicted REE (Mean±SD; kcal/day) | Bias (kcal/ day) | Limits of agreement (±2 SD; kcal/day) | Points outside B-A plot | Paired t-test* | | Correlation** | |
|---|---|---|---|---|---|---|---|---|
| | | | | | t value | P value | r value | P value |
| BIA | 1645±304 | 255 | 377 | 0 | 3.82[a] | 0.007 | 0.793 | 0.019 |
| Cunningham FFM from DXA | 1433±196 | 44 | 203 | 0 | 1.22[a] | 0.261 | 0.876 | 0.004 |
| Cunningham FFM from BIA | 1538±216 | 148 | 273 | 0 | 3.07[a] | 0.018 | 0.793 | 0.019 |
| Wang *et al.* FFM from DXA | 1466±195 | 76 | 203 | 0 | 2.12[a] | 0.072 | 0.875 | 0.044 |
| Wang *et al.* FFM from BIA | 1569±215 | 179 | 273 | 0 | 3.72[a] | 0.007 | 0.792 | 0.019 |

SD: standard deviation
B-A plot: Bland Altman plot
*Comparison between predicted and measured REE
**Correlation between predicted and measured REE
[a] Evaluated on 8 subjects (7 degrees of freedom)

# DISCUSSION

## Purpose

The purpose of this study was to find the best predictive equation for REE for GBM patients and evaluate BIA as a clinical tool for estimating REE and FFM of GBM patients. Measuring REE is the best way to know a patient's caloric needs, but is not always feasible. Many predictive equations for REE exist as a result of statistical models in mostly healthy, sample populations. Predictive equations can use one or a combination of variables, some easily obtained in a clinical setting and others needing more sophisticated measurement methods. The challenge for a clinician is then finding a formula that is best for the population he or she serves. Caloric needs of cancer patients and the changes cancer has on metabolism have become clinical research interests over the last few decades. Many of the predictive equations developed in healthy populations have been tested on cancer patients and other disease states.

BIA is a tool that can estimate FFM, the variable many have found to be a good predictor of REE (29, 33, 35, 36, 39). FFM differs between the sexes (33), naturally decreases as part of the aging process (46), and can vary between people of the same weight. These variables (sex, age, weight) all influence REE and are included in various other predictive equations for REE. One could then postulate that using FFM should eliminate the variability observed in actual REE when predicted by sex, age, and/or weight. The BIA used in this study can do this in two ways: 1) insert estimated FFM into

the equation programmed into the machine and 2) take estimated FFM and use it in other published equations for REE.

BIA has been found to both underestimate FFM (12) and overestimate FFM (14) in comparison to FFM from DXA. In our sample and with the device we used, FFM was overestimated. This study showed FFM from DXA is superior to FFM from BIA in calculating predicted REE by the Cunningham and Wang equations. More DXA and BIA observations are needed before the Cunningham and Wang equations can be compared to equations using easily obtainable clinical variables, such as the Mifflin-St Jeor or HB equations. The results of this study appear to indicate that the Cunningham equation with FFM from BIA may be more accurate than the equation used by the BIA. Once data collection is complete, a more complete data analysis can be done and this will be evaluated.

## Predictive Equations

Of the predictive equations evaluated in this study, the Mifflin-St Jeor equation appears to be the most appropriate method for predicting the REE of GBM patients, due to its low bias, moderate agreement by the Bland Altman approach, and a strong correlation to measured REE. Mifflin-St Jeor is recommended for predicting REE of non-obese and obese healthy individuals due to its ability to better predict REE in a larger number of individuals than any other predictive equation (44, 47). Bauer et al. (32) found in a sample of pancreatic cancer patients Mifflin-St Jeor had the greatest underestimation, but was still accurate at the group level. We found Mifflin-St Jeor slightly overestimated REE, but remained the best predictor of REE in a sample of 15 GBM patients due to it

having the lowest bias and narrowest limits of agreement. The slight differences in the conclusions of this project and Bauer et al. (32) could be related to the narrower age range of their subjects (55-70 years) or that all their subjects were currently normal weight or overweight, with a weight loss greater than 5% of their body weight in the last six months. Our study had a wider age range (35-73 years) and two obese individuals. The different results between these studies could also be due to differences in metabolism of the two cancer sites, the fact that Bauer et al. (32) used repeated observations on four of the same subjects, or the smaller sample size of this project.

## Study Limitations

Certain limitations were placed on the BEAM study due to the patient population with which it deals. Participant accrual was affected by the acceptance process the patient and his or her family must first go through after the diagnosis of an aggressive, malignant tumor (48). Accrual was also affected by the aggressive nature of GBM, especially in the elderly. Individuals who were otherwise eligible did not participate because of the barriers the symptoms of their advanced disease and/or age placed on their ability to participate (49). This resulted in an under representation of the elderly diagnosed with GBM. As mentioned before, the age range of the study could be part of the reason the results differ from others (32). REE is usually lower in the elderly and women (50) and both were well represented in our sample and could have lowered the mean REE for the sample. Sarcopenia, a state of decreased muscle mass and strength observed in some elderly persons (46), can affect REE (33) and of course FFM (46) and was not accounted for in this project.

While the study was designed to be as convenient as possible for the participants and their caregivers, a time commitment remained which many eligible patients decided was not feasible. Commonly reported reasons for deciding not to participate were the additional visits and travel to UAB required by the study or the wish to focus on obtaining standard treatment and not participating in a study which provided no treatment.

Steroid therapy is a part of standard treatment for newly diagnosed GBM patients, yet individuals require varying doses and length of time on steroids to manage their symptoms. Common side effects of steroids include fluid retention, increased appetite, and weight gain (6), all of which were reported by the participants of this study. Steroid dose at the time of first study visit and maximum dose prescribed were both recorded, though not reported or investigated in this project. The effect of steroid dose on REE and nutrition status of GBM patients will be a future direction of the BEAM study.

## Future Directions

Future directions for this project are to include more GBM patients in the analysis for a predictive equation using clinical variables. Also, once more visits with both DXA and BIA are completed, predictive equations using FFM will be compared to predictive equations using clinical variables. After goal recruitment is reached and all subjects have completed a full year of the study, the changes in REE over a year of treatment for GBM will be investigated, along with comparisons of GBM patients to their matched controls.

## Conclusion

Regardless of the predictive equation used, all have limitations. Clinicians should be aware of the range of agreement achieved by the predictive equations they decide to use in their patient population. The results from this study show the predictive equation for BMR programmed into the Biodynamics 310 BIA overestimates REE and should not be used to predict REE in GBM patients. Inserting FFM from BIA into another predictive equation using FFM may show more promising results, and this will be evaluated once data collection is complete. For the time being, the Mifflin-St Jeor equation may be the most appropriate for predicting REE of GBM patients.

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# APPENDIX A

# ORIGINAL IRB APPROVAL FORM

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

*Institutional Review Board for Human Use*

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on September 29, 2013. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

| | |
|---|---|
| Principal Investigator: | NABORS, LOUIS BURT |
| Co-Investigator(s): | BARNHILL, REBECCA V.<br>DARNELL, BETTY E |
| Protocol Number: | **X110128003** |
| Protocol Title: | *A Pilot Study to Determine the Effectiveness of Bioelectrical Impedance Analysis as a Clinical Assessment Tool of Nutrition Status in Glioblastoma Multiforme Patients* |

The IRB reviewed and approved the above named project on 4/15/11. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.

IRB Approval Date: 4-15-11

Date IRB Approval Issued: 4/15/11

Marilyn Doss

Marilyn Doss, M.A.
Vice Chair of the Institutional Review
Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

470 Administration Building
701 20th Street South
205.934.3789
Fax 205.934.1301
irb@uab.edu

The University of
Alabama at Birmingham
Mailing Address:
AB 470
1530 3RD AVE S
BIRMINGHAM AL 35294-0104

# APPENDIX B

# CURRENT IRB APPROVAL FORM

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

*Institutional Review Board for Human Use*

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The Assurance number is FWA00005960 and it expires on August 29, 2016. The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56.

| | |
|---|---|
| Principal Investigator: | NABORS, LOUIS BURT |
| Co-Investigator(s): | BARNHILL, REBECCA V.<br>DARNELL, BETTY E |
| Protocol Number: | **F110128003** |
| Protocol Title: | *A Pilot Study to Determine the Effectiveness of Bioelectrical Impedance Analysis as a Clinical Assessment Tool of Nutrition Status in Glioblastoma Multiforme Patients* |

The IRB reviewed and approved the above named project on 8/24/2011. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received FULL COMMITTEE review.

IRB Approval Date: 8/24/2011

Date IRB Approval Issued: 10-10-11

Identification Number: IRB00000196

Ferdinand Urthaler, MD/RC

Ferdinand Urthaler, M.D.
Chairman of the Institutional Review
Board for Human Use (IRB)

Partial HIPAA Waiver Approved?: Yes

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

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UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

*Institutional Review Board for Human Use*

PI: NABORS, LOUIS BURT
Protocol # F110128003

**UAB IRB Approval of**
**Partial Waiver of HIPAA Authorization**
**to Use PHI in Screening for Research**

☒ **Patient Authorization: Approval of Partial HIPAA Waiver to Use PHI in Screening for Research.** The IRB reviewed the proposed research and granted the request for a "partial HIPAA waiver," to allow the proposed use of protected health information (PHI) in screening for research, based on the following findings:

1. The use/disclosure of PHI to screen candidates for research involves no more than minimal risk to the privacy of individuals
   a. There is an adequate plan to protect the identifiers from improper use and disclosure.
   b. There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.
   c. The PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of PHI would be permitted.
2. The screening cannot practicably be conducted without the waiver or alteration.
3. The screening cannot practicably be conducted without access to and use of the PHI.

**—OR—**

☒ **Full Review**
The IRB reviewed the proposed research at a **convened meeting** at which a majority of the IRB was present, including one member who is not affiliated with any entity conducting or sponsoring the research, and not related to any person who is affiliated with any of such entities. The partial waiver of authorization for screening was approved by the majority of the IRB members present at the meeting.

8-24-11
Date of Meeting

Ferdinand Urthaler, MD/AC
Signature of Chair, Vice-Chair or Designee

10-10-11
Date

☐ **Expedited Review**
The IRB used an **expedited review procedure** because the research involves no more than minimal risk to the privacy of the individuals who are the subject of the PHI for which use or disclosure is being sought. The review and approval of the partial waiver of authorization for screening was carried out by the Chair of the IRB, or by one of the Vice-Chairs of the IRB as designated by the Chair of the IRB.

_____
Date of Expedited Review

_____
Signature of Chair, Vice-Chair or Designee

_____
Date

# APPENDIX C

# CONSENT FORM FOR GBM CASES

UAB

# Informed Consent Document: CASE GROUP

**TITLE OF RESEARCH:** A Pilot Study to Determine the Effectiveness of Bioelectrical Impedance Analysis as a Clinical Assessment Tool of Nutrition Status in Glioblastoma Multiforme Patients (The BEAM Study [BIA Effectiveness as Assessment Tool for GBM Patients])

**IRB PROTOCOL:** **F110128003**

**PRINCIPAL INVESTIGATOR:** Louis Burt Nabors, MD
**OTHER INVESTIGATORS:**
Rebecca Barnhill, RD
Betty Darnell, MS, RD, LD, FADA
Richard Taylor, CRNP
Katherine Mange, CRNP
Cathy Casey, MSN, CRNP

**SPONSOR:** University of Alabama at Birmingham Neuro-oncology Division

## INTRODUCTION

This is a research study to look at the use of Bioelectrical Impedance Analysis (BIA), a quick, portable, and noninvasive tool to estimate your body composition and energy needs, as a clinical nutritional assessment tool. Other nutrition measurements and their affect on your tumor will be collected. You are being asked to take part in this study because you have a new diagnosis of a brain tumor called a glioblastoma multiforme (GBM). This is a Pilot study. A Pilot study is a small research study done before a larger study to check the design and feasibility of the study.

## PURPOSE OF STUDY

You are being asked to participate in a research study designed to evaluate how the composition of your body (the amount of fat and muscle) as determined by BIA can predict the progression and outcomes of your tumor. Little is known about body composition or the calorie needs of GBM patients after diagnosis and during treatment. New therapies are under investigation to increase life expectancy of GBM patients, but little has been documented about the nutritional concerns of this type of tumor and how they impact life expectancy and quality of life. We want to know more about body composition, nutrition status, and calorie needs so we can find possible ways to improve outcomes for GBM patients.

## HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Approximately 20 patients with GBM and 20 subjects who do not have GBM, but will serve as a control group for the research, will take part in this study at UAB.

UAB IRB
Date of Approval 1-19-12
Not Valid On 8-24-12


Participant's initials_____

**STUDY PROCEDURES**

If you agree to participate in this study, the study coordinator will try to schedule most of your study visits when you are already here for your regular scheduled clinic visits. Some study visits may require you to come in on a day when you do not have a clinic visit. The study coordinator will try to schedule all your study visits when most convenient for you. For women of childbearing age, a negative pregnancy test must be confirmed before enrolling in this study.

**Explanation of Study Procedures:**

- **Nutrition Assessment:** A dietitian will ask you questions about changes in your weight and food intake, if you have any gastrointestinal symptoms (diarrhea, vomiting, etc.), and if your activity is limited. The dietitian will also ask if you have noticed recent reduction in the size of your muscles or edema (swelling from fluid). This will take approximately 15 minutes.
- **Bioelectrical Impedance Analysis:** Bioelectrical impedance analysis (BIA) is a quick, portable, and noninvasive tool to estimate body composition. Handheld BIA machines are used by many people in their homes or at gyms to measure their body fat and muscle mass. It works by sending a small flow of electrical current between your right hand and foot. The current used is low and below the level that can be felt. Before the test, you will need to remove your shoes, socks or hosiery. An alcohol prep wipe will be used to clean the area where the electrodes will be placed. Two electrodes with a sticky backing, similar to a band-aid, will be placed on your right hand and two on your right foot. You will then lie flat on your back and rest for 15 minutes before the test is done. This allows your body to relax and will give a more accurate measurement. Then, the dietitian will attach wires to the electrodes, turn the machine on and enter your gender, height, weight and age. You will need to lie still with the inside of your legs not touching and your arms not touching your sides for approximately 3 minutes. The total time to complete a BIA, including rest period and placing the electrodes, is approximately 20 minutes. We will not perform a BIA if you have a pacemaker or other implanted electrical device or are pregnant. Please let us know if you have one of these devices or could be pregnant.
- **Dual-Energy X-ray Absorptiometry (DXA) scan:** For this test, you will lie still on a padded table while a machine scans your body. The machine uses low-level X-rays to measure body fat and muscle. The test will take 10 to15 minutes. It will take place at the Kirklin Clinic. It is a short walk from the UAB Hospital and Clinical Research Unit (CRU).
- **Resting Energy Expenditure:** Resting energy expenditure (REE) is a measurement of the calories your body burns at rest. A test to determine your REE will be done at the UAB Clinical Research Unit. You will need to complete a 12 hour fast for this test. You must not eat or drink anything and have no caffeine for 12 hours before the test. You may drink water. To conduct this test, you will lie in a hospital bed with a clear plastic bubble placed over your head and shoulders for 30 minutes. The bubble will collect and measure the air you breathe.

You will be able to breathe normally. A standard breakfast will be provided to you after the test, at no cost to you. This test will take approximately 30 minutes.

- **Blood Draw:** Your DNA information and plasma will be collected from a blood draw, if you choose to allow us to use this information. About 10 ml (or 2 tablespoons) of blood will be collected. This information will be used to study genes that affect cancer and how diet can influence these genes. This collection will take approximately 5 minutes, and may be collected at either a standard care appointment or study visit.
- **Stool Sample:** You may choose not to provide stool samples. If you choose to provide stool samples, you will collect a sample of your stool in an in-home collection kit we will provide you. A short Information Form with questions about factors that can affect your gut bacteria will be included for you to answer. It will take about 5 minutes to answer the questions. You will then use the pre-addressed and postage paid envelops to mail it to us. From your stool sample we will collect the bacteria that live in your gut. We want to look at how the type and number of bacteria in your gut affects your energy needs and how cancer treatment affects the bacteria.
- **Medical records information:** A researcher will look at your hospital and clinic medical chart for information related to your tumor and overall health. These information includes Karnofsky Performance Status Scale (KPS), European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QOL) questionnaires, your cancer therapies (type and dates received), serum albumin (from blood draws ordered by your doctor), steroid dose prescribed by your doctor, height and age. The dietitian will also look for your most recent weight and reported muscle wasting and changes in food intake, appetite, and taste.

If a recent serum albumin or EORTC Quality of Life questionnaire is not in your medical record, they may be completed at a study visit. Albumin will be collected by a blood draw of about 3.5 ml (or less than 1 teaspoon) of blood.

**Explanation of Study Visits:**

First Study Visit: A study researcher will meet you at the UAB Clinical Research Unit (CRU) to go over the study procedures and this consent form with you. For women of childbearing age, a urine pregnancy test will be completed. You will not be allowed to participate if you are pregnant. This visit will last approximately 1 hour and half. A visit to the Kirklin Clinic for a DXA scan will be scheduled the same day or around the same time and will last approximately 30 minutes. At this visit you will have:

- Nutrition assessment
- Bioelectrical Impedance Analysis
- Resting Energy Expenditure
- DXA (may be performed at separate visit)
- Stool sample (optional)
- Blood draw for DNA and plasma (optional)
- Relevant information will be pulled from your medical record

3 Month Study Visit: Approximately 3 months after your first visit. The dietitian will meet you at your regularly scheduled follow-up appointment at the Kirklin Clinic Brain Tumor Center or will make an appointment for you at the CRU if there are time conflicts. Your time with the dietitian will last approximately 30 minutes. You will have:

- Nutrition assessment
- Bioelectrical Impedance Analysis
- Relevant information will be pulled from your medical record

6 Month Visit: Approximately 6 months after your first visit, you will come to the Clinical Research Unit (CRU), which is located at UAB Hospital, the same day or within one week of your regularly scheduled follow-up appointment at the Kirklin Clinic Brain Tumor Center. Your stay at the CRU will be approximately 1 hour and a half. You will have:

- Nutrition assessment
- Bioelectrical Impedance Analysis
- Resting Energy Expenditure
- Stool sample (optional)
- Relevant information will be pulled from your medical record

9 Month Visit: Approximately 9 months after your first visit. The dietitian will meet you at your regularly scheduled follow-up appointment at the Kirklin Clinic Brain Tumor Center or she will make an appointment for you at the CRU if there are time conflicts. Your time with the dietitian will last approximately 30 minutes. You will have:

- Nutrition assessment
- Bioelectrical Impedance Analysis
- Relevant information will be pulled from your medical record

12 Month Visit: Approximately 12 months after your first visit, you will come to the Clinical Research Unit (CRU), which is located at UAB Hospital, the same day or around the time of your regularly scheduled follow-up appointment at the Kirklin Clinic Brain Tumor Center. Your stay at the CRU will be approximately 1 hour and a half. You will have:

- Nutrition assessment
- Bioelectrical Impedance Analysis
- Resting Energy Expenditure
- Stool sample (optional)
- Relevant information will be pulled from your medical record

**A summary of all the study visits is on the next page.**

**Table 1: Summary of study visits**

| Baseline | 3-month | 6-month | 9-month | 12-month |
|---|---|---|---|---|
| -Informed Consent<br>-Pregnancy Test<br>-Weight and height<br>- Nutrition assessment<br>-BIA<br>-REE<br>-DXA scan<br>- Blood draw for DNA and plasma*<br>-Stool sample*<br>-Medical chart review | - Weight and height<br>-BIA<br>- Nutrition assessment<br>-Medical chart review | - Weight and height<br>-BIA<br>-REE<br>- Nutrition assessment<br>-Stool sample*<br>-Medical chart review | - Weight and height<br>-BIA<br>- Nutrition assessment<br>-Medical chart review | - Weight and height<br>-BIA<br>-REE<br>- Nutrition assessment<br>-Stool sample*<br>-Medical chart review |
| Length of study visit ~1.5 hour plus ~ 30 minutes for DXA scan | Length of study visit ~30 minutes | Length of study visit ~1.5 hour | Length of study visit ~30 minutes | Length of study visit ~1.5 hour |

*You may choose to not participate in these procedures.

**REFUSAL OR WITHDRAWAL WITHOUT PENALTY**

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this institution.

If you are a UAB student or employee, taking part in this study is not a part of your UAB class work or job duties. You can refuse to enroll or withdraw from the study at anytime without affecting your class standing, grades or job at UAB. Your will not be offered or receive any special considerations if you take part in this research.

**RISKS AND DISCOMFORTS**

- **Bioelectrical Impedance Analysis** – The electrical current used by the BIA is low and below the level that can be felt. There should be no discomfort other than having the electrodes placed and removed from your hand and foot. Removal of the sticky electrodes is easier than removing a band-aid. ***If you have an implanted pacemaker or are pregnant you should not take part in this study because of the possible risk of injury from even a small current of electricity.***

- **Resting Energy Expenditure** - The REE may cause a feeling of claustrophobia because a plastic bubble will be placed over your head and shoulders. To overcome this feeling, the clear plastic bubble allows you to see through and it will not restrict your breathing.

- **Blood Draws** - You may experience some discomfort when the blood samples are taken by drawing blood from a vein in your arm. Risks of blood draws include

pain, infection, bruising at the puncture site, and fainting. To reduce these risks, your blood will be drawn only by a trained nurse. About 3.5 ml (or less than 1 teaspoon) of blood will be needed if a recent serum albumin is missing from your medical record. For DNA and plasma collection about 10 ml (or about 2 tablespoons) will be collected once.

- **Whole body DXA scanning** will expose you to a low level of background radiation. This exposure is equivalent to about 4 to 5 days of the low-level of radiation that is found naturally in our environment.

- The biggest inconvenience will be your time. Participating in this study requires you to be at the CRU for 3 visits, lasting approximately 1 hour and half each, and an additional 30 minute visit to the Kirklin Clinic. All other visits will add about 30 additional minutes to your regularly scheduled appointments or will require a 30 minute study visit to the CRU. To minimize this inconvenience, the study coordinator will try to schedule your study visits around your usual schedule as much as possible.

**INFORMATION FOR WOMEN OF CHILDBEARING POTENTIAL**
If you are pregnant or become pregnant, there may be risks to the embryo or fetus from the DXA scanning and BIA measurements. You will be excluded from the study if you have a positive pregnancy test.

**BENEFITS**
If you agree to take part in this study, there may or may not be direct medical benefit to you. If we find any changes in your nutritional status, we will discuss them with you. We hope the information learned from this study will benefit other subjects with brain tumors in the future.

**ALTERNATIVES**
This study does not provide treatment. The alternative to this study is to not participate.

**CONFIDENTIALITY**
Information obtained about you for this study will be kept confidential to the extent allowed by law. All records pertaining to your medical history and participation in this study will be recorded by study number only, in order to protect your confidentiality. However, research information that identifies you may be shared with the UAB Institutional Review Board (IRB) and others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of the Office of Human Research Protections (OHRP). The results of the research may be published for scientific purposes; however, only group information without personal identifiers will be included when this study is submitted for publication. These results could include your disease progression, lab tests, body composition, nutritional status, and resting energy expenditure results.
If you receive services in University Hospital as part of this study, this informed consent document will be placed in and made part of your permanent medical record at this facility.

**COSTS OF PARTICIPATION**
There will be no additional costs to you to participate in this research study. Some study-related examinations and tests are also part of your routine care at the Kirklin Clinic Brain Tumor Center. The costs for your standard medical care will be billed to you and/or your insurance company in the usual manner. The additional study-related examinations and tests (BIA, DXA scan, stool sample analysis, REE, and Nutrition Assessment) will be provided at no cost during the study.

**PAYMENT FOR PARTICIPATION IN RESEARCH**
You will receive a $50 Gift Card after completing the first study visit, 6-month visit, and 12-month visit, for a possible total payment of $150.

**PAYMENT FOR RESEARCH-RELATED INJURYS**
UAB has not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

**SIGNIFICANT NEW FINDINGS**
You will be told by your doctor or his staff if new information becomes available and might affect your choice to stay in the study.

**QUESTIONS**
If you have any questions, concerns, or complaints about the research, please call Dr. Burt Nabors or Ms. Rebecca Barnhill. They will be happy to answer your questions. Dr. Nabors can be reached at (205) 934-1432 and Ms. Barnhill can be reached at (205) 975-8341.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the Office of the Institutional Review Board for Human Use (OIRB) at (205) 934-3789 or 1-800-822-8816. If calling the toll-free number, press the option for "all other calls" or for an operator/attendant and ask for extension 4-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

**GENETIC ANALYSIS**
If you provide your DNA information, the DNA that composes your genes will be analyzed and that data, which is referred to as your genotype or complete genetic makeup, will be compared to your phenotype, which consists of your observable traits, characteristics, and diseases. The aim of this research is to discover genetic factors that contribute to the development, progression, or treatment for GBM, other brain tumors, other cancers. Your sample will be coded with a number and the lab analyzing this information will not be able to identify you. Your genotype and phenotype data will be for research purposes.

A new federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most

employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

**STORAGE OF SPECIMENS FOR FUTURE RESEARCH USE**

Upon entering the study, you will be assigned a unique identifying code that does not contain identifying information. Subsequently, all DNA, plasma, and stool samples will be identified using this code. Only the study investigators and the IRB will have access to this information. The aim of this research is to discover genetic factors that contribute to the development, progression, or treatment and therapy for brain tumors. The blood and stool samples will be stored at UAB, and if you agree, may be used for future research and may be shared with other investigators.

We request your permission to store samples for future research. Future studies using stored samples will likely focus on brain tumors and calorie needs. However, it could be possible that other diseases such as other types of cancer and cancer treatments would also be studied.

You may choose not to provide your blood for DNA information and blood plasma and/or stool samples and still participate in this study.

Please initial your choices below:

_____ I WILL NOT provide my stool samples for this research study.

_____ I WILL provide stool samples for this research study.

_____ I AGREE to allow my stool samples to be kept and used for future research.

_____ I DO NOT agree to allow my stool samples to be kept and used for future research.

_____ I DO NOT agree to the collection of my DNA information and blood plasma.

_____ I AGREE to the collection of my DNA information and blood plasma.

_____ I AGREE to allow my DNA information and blood plasma to be kept and used for future research.

_____ I DO NOT agree to allow my DNA information and blood plasma to be kept and used for future research.

**LEGAL RIGHTS**
You are not giving up any of your legal rights by signing this consent form.

**SIGNATURES**
Your signature below indicates that you agree to participate in this study. You will receive a copy of this signed informed consent. You may also request a copy of the protocol (full study plan).

Signature of Participant Date

Signature of Principal Investigator or Person Obtaining Consent Date

Signature of Witness Date

## University of Alabama at Birmingham
## AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION FOR RESEARCH

---

**What is the purpose of this form?** You are being asked to sign this form so that UAB may use and release your health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your health information may be used for the research.

Participant name: _____
Research Protocol: A Pilot Study to Determine the Effectiveness of Bioelectrical Impedance Analysis as a Clinical Assessment Tool of Nutrition Status in Glioblastoma Multiforme Patients

UAB IRB Protocol Number: F110128003
Principal Investigator: Dr. Louis B. Nabors, III
Sponsor: Neuro-Oncology Division

**What health information do the researchers want to use?** All medical information and personal identifiers including past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind related to or collected for use in the research protocol.

**Why do the researchers want my health information?** The researchers want to use your health information as part of the research protocol listed above and described to you in the Informed Consent document.

**Who will disclose, use and/or receive my health information?** The physicians, nurses and staff working on the research protocol (whether at UAB or elsewhere); other operating units of UAB, HSF, UAB Highlands, The Children's Hospital of Alabama, Callahan Eye Foundation Hospital and the Jefferson County Department of Public Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees; and outside regulatory agencies, such as the Food and Drug Administration.

**How will my health information be protected once it is given to others?** Your health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

**How long will this Authorization last?** Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

**Can I cancel the Authorization?** You may cancel this Authorization at any time by notifying the Director of the IRB, in writing, referencing the Research Protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the health information that was provided before you cancelled your authorization.

**Can I see my health information?** You have a right to request to see your health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of participant: _____ Date:_____
**or** participant's legally authorized representative:_____ Date:_____
Printed Name of participant's representative:_____
Relationship to the participant:_____