Acral Lentiginous Melanoma

Incidence and Survival Patterns in the United States, 1986-2005

Porcia T. Bradford, MD; Alisa M. Goldstein, PhD; Mary L. McMaster, MD; Margaret A. Tucker, MD

**Objective:** To examine incidence and survival patterns of acral lentiginous melanoma (ALM) in the United States.

**Design:** Population-based registry study. We used the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute to evaluate data from 17 population-based cancer registries from 1986 to 2005.

**Participants:** A total 1413 subjects with histologically confirmed cases of ALM.

**Main Outcome Measure:** Incidence and survival patterns of patients with ALM.

**Results:** The age-adjusted incidence rate of ALM overall was 1.8 per million person-years. The proportion of ALM among all melanoma subtypes was greatest in blacks (36%). Acral lentiginous melanoma had 5- and 10-year melanoma-specific survival rates of 80.3% and 67.5%, respectively, which were less than those for all cutaneous malignant melanomas overall (91.3% and 87.5%, respectively; *P* < .001). The ALM 5- and 10-year melanoma-specific survival rates were highest in non-Hispanic whites (82.6% and 69.4%), intermediate in blacks (77.2% and 71.5%), and lowest in Hispanic whites (72.8% and 57.3%) and Asian/Pacific Islanders (70.2% and 54.1%). Acral lentiginous melanoma thickness and stage correlated with survival according to sex and in the different racial groups.

**Conclusions:** Population-based data showed that ALM is a rare melanoma subtype, although its proportion among all melanomas is higher in people of color. It is associated with a worse prognosis than cutaneous malignant melanoma overall. Hispanic whites and Asian/Pacific Islanders have worse survival rates than other groups, and factors such as increased tumor thickness and more advanced stage at presentation are the most likely explanations.


**CUTANEOUS MALIGNANT melanoma (CMM) is the most lethal form of skin cancer and accounts for approximately 78% of all skin cancer deaths. In the United States, the incidence of CMM has been increasing rapidly, and currently, CMM is the sixth and seventh most commonly diagnosed cancer among men and women, respectively.**

According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, the estimated incidence of CMM in the United States in 1973 was 6.8 per 100,000 person-years, and this rate increased to 20.8 per 100,000 in 2005. This increase in incidence is among the highest in SEER, with the exception of lung cancer in women. There are 4 major histologic subtypes of CMM. Superficial spreading melanoma (SSM) is the most common subtype, accounting for approximately 70% of cases, and occurs most often on the trunk. Nodular melanoma (NM) accounts for about 15% of melanomas and has only a vertical growth phase. Lentigo maligna melanoma (LMM) accounts for 13% of melanomas and correlates with long-term sun exposure in fair-skinned older individuals. Acral lentiginous melanoma (ALM) occurs predominantly on the nail beds, palms, and soles.

Acral lentiginous melanoma accounts for about 2% to 3% of all melanomas. The overall incidence of CMM in darker-skinned individuals is low compared with whites; however, ALM makes up a much higher proportion of CMM in darker-skinned individuals (ie, blacks, Asians, and Hispanics). In 1976, Reed first described ALM as pigmented lesions on the extremities, particularly on plantar regions, like the palms of the hands and soles of the feet, that are characterized by a lentiginous (radial) growth phase evolving over months or years to a dermal (vertical) invasive stage.

**Author Affiliations:** Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.
This was in contrast to CMM overall, which is generally found on sun-exposed areas. Arrington et al² were the first to note that this type of melanoma was the most common expression of melanoma in blacks and that patients with ALM had a very poor prognosis. In Reed’s study,⁴ patients with ALM had a mean 3-year survival rate of 11%. The poor survival rate of these patients may have been due in part to delays in diagnosis.

Several single-institution case series of ALM have been published.⁶⁻¹¹ However, because this subtype of melanoma is rare, these studies have been limited by small sample sizes and have not been population-based. There have been recent population-based studies on CMM overall in ethnic populations.¹²⁻¹⁴ However, these studies have not focused specifically on ALM and its incidence and survival patterns. Hence, the purpose of this study was to conduct a population-based evaluation of ALM to determine its current incidence and survival patterns in the United States. We also examined ALM tumor characteristics, such as tumor thickness and stage, which might affect prognosis.

METHODS

We used the SEER program to derive incidence, frequency, and survival data for 1413 histologically confirmed invasive cases of ALM reported to 17 cancer registries from 1986 to 2005.² Beginning in 1986, consistent data on ALM were available from 17 population-based registries that together represent approximately 26% of the US population. The 17 registries include 11 states (Alaska, greater California, Connecticut, rural Georgia, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah) and 6 standard metropolitan areas (Atlanta, Georgia; Detroit, Michigan; Los Angeles, San Francisco–Oakland, and San Jose–Monterey, California; and Seattle–Puget Sound, Washington). The SEER coverage includes approximately 23% of the US non-institutional population, with the exception of Hawaii, Iowa, Kentucky, Louisiana, New Jersey, and New Mexico. Patients were identified using the World Health Organization’s International Classification of Diseases for Oncology. Version 3 (ICD-O-3) morphology code for ALM (8744/3).¹⁵ All patients reported to SEER had their tumors confirmed histologically.

We calculated age-adjusted (2000 US standard)¹⁶ incidence rates using the SEER*Stat software public-use program, version 6.3.5;¹⁷ incidence rates were expressed as new cases per 1 000 000 person-years and were analyzed by age, sex, race, anatomic site of presentation, year of diagnosis, melanoma thickness, and stage at diagnosis. Acrul lentiginous melanoma incidence and frequency data were compared with CMM overall (n=88 885), which included all other melanoma histologic subtypes reported to SEER. The melanoma histologic subtypes in the CMM category included superficial spreading, nodular, lentigo maligna, balloon cell, amelanotic, desmoplastic, mucosal lentiginous, mixed epithelioid/spindle cell, epithelioid, and spindle cell melanomas.

Tumors designated as ALM were not included in the CMM category. Melanomas classified as “not otherwise specified (NOS)” (ICD-O-3 code 8720/3; n=71 099) were excluded from the analyses. Exclusion of the NOS melanomas had no statistically significant effects on the results (data not shown). Because of small numbers of ALM, American Indians and Alaska Natives (n=11) and patients designated as being of an “unknown” race (n=17) were excluded from the study. Anatomic sites of presentation were compiled according to ICD-O-3 topography codes. Specific sites included skin of the upper limb, including the hand (C44.6), and skin of the lower limb, including the feet (C44.7). All other anatomic sites of ALM reported to SEER (n=74) were excluded from this study.

Breslow thickness is a continuous variable and is the most important prognostic factor in cutaneous melanoma.¹⁴⁻¹⁵ Tumor thickness as measured by the Breslow technique was divided into the following 4 categories: 0.01 to 1.00 mm, 1.01 to 2.00 mm, 2.01 to 4.00 mm, and thicker than 4.00 mm. The SEER thickness data were available only for tumors diagnosed after 1988. The extent of SEER disease information determined stage of disease at diagnosis.¹³⁻²² Stage at diagnosis was defined according to the American Joint Committee on Cancer (AJCC) staging system.²¹ Only those patients with adequate pathology information were selected for stage analyses. Patients with melanoma whose tumor sizes were thinner than 1.0 mm with or without ulceration or whose tumors were thinner than 2.0 mm without ulceration were coded as stage I. Tumors thicker than 1.0 mm with ulceration and nonulcerated tumors thicker than 2.0 mm were coded as stage II. Tumors of any size with positive regional lymph node involvement were coded as stage III. Tumors of any size with metastatic involvement were coded as stage IV.

Cause-specific survival is a measure of net survival that is calculated by using the cause of death listed on the death certificate to estimate the proportion of deaths caused by a cancer. For these analyses, melanoma-specific survival rates were calculated using the survival module of the SEER*Stat software, version 6.3.5.²³ Both 5- and 10-year melanoma-specific survival rates were calculated. Standard SEER exclusion criteria for the survival analyses included diagnosis of other cancers prior to diagnosis of ALM and missing survival information.

Time trends were evaluated with the use of SEER*Stat software, version 6.3.5,¹⁷ using incidence rates per 1 000 000 age-adjusted to the 2000 US Standard Population.¹⁸ Ninety-five percent confidence intervals (CIs) for incidence rates and trends were calculated using the modification of Fay et al.¹⁹ Annual percentage change (APC) over time was calculated using the weighted least-squares method. The measures of association between incidence rate and race were analyzed with PROC FREQ software (version 9.1.3 for Windows; SAS Inc, Cary, North Carolina), using the Pearson χ² test. Results with P<.05 were regarded as significant. All statistical tests were 2-sided. Kaplan-Meier estimates were used to compare survival between different racial groups. We used PROC LIFETEST software (version 9.1.3; SAS Inc) to test for differences in survivor function using the Wilcoxon rank sum test.

RESULTS

INCIDENCE AND DEMOGRAPHIC DATA

Microscopically confirmed ALM was diagnosed in 1413 residents of 17 SEER registry areas from 1986 to 2005, compared with 88 885 residents with CMM overall (excluding NOS). The proportion of ALM among all melanoma subtypes was greatest in people of color (Figure 1), accounting for 36% of all CMM in blacks, 18% in Asian/Pacific Islanders, 9% in Hispanic whites, and only 1% in non-Hispanic whites. The overall age-adjusted incidence rate of ALM for the SEER 17 cancer registries was 1.8 per 1 000 000 person-years. The incidence rates for the other major melanoma histologic subtypes were as follows: 12.0 per 1 000 000 person-years for LMM, 12.7
per 1,000,000 person-years for NM, and 57.4 per 1,000,000 person-years for SSM.

The incidence rates of ALM in men and women were similar (1.9 and 1.8 per 1,000,000 person-years, respectively). Interestingly, the incidence rates for ALM were similar in non-Hispanic whites and blacks (1.8 per 1,000,000 person-years). Hispanic whites had statistically significant higher incidence rates of ALM (2.5 per 1,000,000 person-years; \( P = .007 \)) compared with non-Hispanic whites. Asian/Pacific Islanders had statistically significant lower incidence rates of ALM (1.1 per 1,000,000 person-years; \( P = .002 \)) compared with non-Hispanic whites.

The mean age at diagnosis for ALM was 62.8 years, compared with 58.5 years for CMM overall. The mean age at ALM diagnosis for men was 63.1 years, and for women, 62.2 years. Incidence also significantly increased with each year of advancing age, from 0.1 per 1,000,000 person-years in adolescents (<20 years old) to 9.3 per 1,000,000 person-years in the elderly (80-84 years old), with a yearly percentage change of 6.0 \( (P < .001) \). Incidence also increased with each year of advancing age in both men and women (Figure 2A). Men had a yearly percentage change of 8.3 \( (P < .001) \), and women had a yearly percentage change of 5.0 \( (P < .001) \). The male age-specific incidence rates nearly doubled those of women after age 80 years. The increase in incidence with each year of advancing age was also seen across the different racial groups (Figure 2B), with Hispanic white age-specific rates nearly doubling those of non-Hispanic whites and tripling the rate of Asian/Pacific Islanders after age 70 years.

The SEER 13 data from the years 1992 to 2005 were used to look at temporal trends in ALM, because Hispanic origin was first systematically recorded in SEER in 1992. The incidence rate of ALM increased slightly from 1.6 per 1,000,000 person-years (95% CI, 1.3-1.9) during 1992 to 1994 to 2.1 per 1,000,000 person-years (95% CI, 1.8-2.5) for 2004 to 2005 \( (P = .02) \). Figure 3 shows that rates for Hispanic whites increased from 1992 to 1998. Non-Hispanic whites, Hispanic whites, and blacks all increased in incidence after 2003, but these rises were not statistically significant \( (P = .10, P = .16, \text{ and } P = .08, \text{ respectively}) \). Asian/Pacific Islanders had the lowest incidence rates of the 4 racial groups throughout the time period.

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**Figure 1.** Distribution of major melanoma histologic subtypes by race using Surveillance, Epidemiology, and End Results (SEER 17) registries, 1986 to 2005. “Other” includes all additional melanoma histologic subtypes coded by SEER, including balloon cell, amelanotic, desmoplastic, mucosal lentiginous, mixed epitheloid/spindle cell, epitheloid, and spindle cell melanomas.

**Figure 2.** Age-specific incidence rates of acral lentiginous melanoma. Rates by decade based on sex (A) and race (B). Incidence rates are based on the Surveillance, Epidemiology, and End Results (SEER 17) registries, years 2000 to 2005, and reported per 1,000,000 person-years and age-adjusted to the US 2000 standard. \( \text{A/PI indicates Asian/Pacific Islander.} \)

**Figure 3.** Age-adjusted incidence rates of acral lentiginous melanoma by year of diagnosis based on race. Incidence rates are based on the Surveillance, Epidemiology, and End Results (SEER 13) registries (1992-2005) and reported per 1,000,000 person-years and age-adjusted to the US 2000 standard. \( \text{A/PI indicates Asian/Pacific Islander.} \)
SITE DISTRIBUTION

Most ALMs (~78.3%) were found on the skin of the lower limb. Twenty-two percent of ALMs were found on skin of the upper limb. These percentages were similar in men and women, with 76.1% of ALMs found on the lower limb in men, and 80.1% in women. Among racial groups, blacks had the highest percentage of ALMs occurring on the lower limb (83.6%), followed by Hispanic whites (82.6%), Asian/Pacific Islanders (77.8%), and non-Hispanic whites (77.0%). In contrast, for CMM overall, most tumors were found on the trunk (38.7%), followed by upper limbs (24.0%), lower limbs (22.4%), and the head and neck (11.7%). The anatomic sites for CMM were also sex dependent, with most CMMs occurring on the trunk in men (47.4%) and the lower limbs in women (35.9%). Among racial groups, the most frequent location for CMM was on the lower limbs in blacks (64.0%), Asian/Pacific Islanders (46.7%), and Hispanic whites (36.4%). By contrast, CMMs occurred more frequently on the trunk (38.9%) in non-Hispanic whites.

CHARACTERISTICS OF TUMORS

Because tumor thickness is the most important prognostic indicator in all types of melanoma, we evaluated tumor thickness for CMM and ALM. Overall, CMMs were thinner than ALMs, with 70.0% of CMMs diagnosed at 0.01 to 1.00 mm. In contrast, for ALMs, only 41.3% were diagnosed at 0.01 to 1.00 mm, and 37.0% were diagnosed at thicker than 2.00 mm (Table 1). Tumor thickness at diagnosis varied by sex. Men (45.3%) were more likely than women (30.6%) to have ALMs that were thicker than 2.00 mm at diagnosis, whereas more women than men tended to have 0.01- to 1.00-mm tumors at diagnosis (45.5% and 35.7%, respectively). Non-Hispanic whites had the highest percentage of thin ALMs, with 43.0% diagnosed at 0.01 to 1.00 mm. The highest percentage of thick ALMs (>4.00 mm) was seen in Asian/Pacific Islanders (22.0%) (Table 2).

We also compared stage at diagnosis, another important prognostic indicator, among ALMs and CMMs. Approximately 37.8% of ALMs were stage I, in contrast to 67.9% of CMMs (Table 1). In men, 30.0% of ALMs were diagnosed at stage I compared with 41.9% in women. This distribution by stage among men and women was significantly different (P < .001; data not shown). As expected, similar to the patterns observed for tumor thickness, non-Hispanic whites had the highest percentage of ALM diagnosed at stage I (40.1%), and Asian/Pacific Islanders had the highest percentage of ALM diagnosed at stage III (50.0%) (Table 2).

SURVIVAL

Overall, patients with ALM had 5- and 10-year melanoma-specific survival rates of 80.3% (95% CI, 77.6-83.0) and 67.5% (95% CI, 63.4-71.6), respectively. These rates were lower than for CMM overall, which had 5- and 10-year survival rates of 91.3% (95% CI, 91.1-91.5; P < .001) and 87.5% (95% CI, 87.1-87.9; P < .001), respectively (Table 1 and Figure 4A). When controlled for thickness, CMM 10-year survival rates at 0.01 to 1.00 mm and 2.01 to 4.00 mm were significantly lower than respective CMM 10-year survival rates (see Table 1 for P values). When controlled for stage, ALM 10-year survival rates at stages II and III were also significantly lower than respective CMM 10-year survival rates (see Table 1 for P values). Women had statistically significantly higher 5- and 10-year melanoma-specific survival rates than men (85.6% [95% CI, 82.3-88.9], and 76.2% [95% CI, 71.3-81.1] compared with 73.8% [95% CI, 69.3-78.3], P < .001 and 56.7% [95% CI 49.8-63.6], P < .001). However, when we controlled ALM for tumor thickness or stage, there was no statistically sig-
Acral lentiginous melanoma is the least frequent of the 4 major histologic subtypes of CMM overall; however, it comprises a higher percentage of total melanoma in people of color. Acral lentiginous melanoma was first described in the late 1970s and was not documented by SEER as a distinct melanoma histologic subtype until 1986. The distinct histologic and phenotypic characteristics of ALM, in conjunction with its higher proportion of melanoma subtypes in blacks, Hispanics, and Asians, has fostered speculation that this histologic variant of melanoma might differ biologically from its counterparts. However, accurate assessment of ALM in the United States has been difficult because ALM accounts for such a small proportion of melanomas.24 To our knowledge, this study is the largest population-based evaluation of ALM yet conducted. We provide new data, particularly regarding Hispanic whites and Asian/Pacific Islanders, on current incidence and survival patterns in the United States.

The proportion of ALM among all melanoma subtypes was greatest in people of color, with blacks having the highest percentage (36%). These results are in contrast to previous studies showing that SSM was the most common histologic subtype for all racial groups, including blacks.12,13 It is important to note that our study included all SEER registry areas, representing approximately 26% of the US population. We also include the latest data from the years 2004 and 2005. Zell et al13 showed trends for melanoma in the state of California from 1993 to 2003, representing roughly 12% of the US population. Cormier et al12 showed trends for melanoma in the SEER 11 registries from 1992 to 2002, representing about 14% of the US population.

The incidence of ALM in the United States has remained relatively steady over time, unlike CMM overall, the incidence of which has been steadily increasing. During the 1970s, the incidence rate of CMM increased rapidly by about 6% per year.1 Since 1981, the rate of increase has slowed to 1% to 3% per year. The steady increase in CMM incidence is most likely due to increased UV radiation, even though increased surveillance, physician and patient education, and sun safety measures have dramatically slowed the rate of increase.

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prelesional trauma (ie, puncture wounds, stone bruises, burns) were reported in 13% of 119 patients and 25% of 35 patients. In a predilection for acral locations, especially on plantar regions. This also seemed to be true in our study, in which the most frequent locations for ALM were on the lower limbs in all racial groups. This predilection for ALM on plantar locations has led many to believe that trauma may be important in the etiology for ALM, because sun exposure has not been shown to be a risk factor for ALM. Most ALM lesions are found on the lower limbs, even though the surface area of the palms and soles is similar. The sole of the foot is constantly exposed to pressure, friction, maceration, and irritation. In 2 retrospective ALM case series in which a trauma history was taken, 13% of 119 patients and 25% of 35 patients’ reported prelesional trauma (ie, puncture wounds, stone bruises, friction blisters, contact dermatitis). Arguments against the trauma theory include the fact that the hand is exposed to more UV light and acute trauma. Furthermore, no change in incidence of melanoma of the soles was seen when African tribes became urbanized and began to wear shoes. Another factor that may play a role in the predilection of ALM for plantar locations is the fact that the density of melanocytes is 50% higher there than on the palm.

Thickness and stage are important prognostic indicators for melanoma. Overall, about 70.0% of CMMs were thin (0.01-1.00 mm) at diagnosis, and 67.5% were stage I. In contrast, only 41.3% of ALMs were classified as thin, and 37.8% were stage I. Acral lentiginous melanoma had significantly poorer melanoma-specific survival rates when compared with CMM overall (P < .001). The distribution of thickness and stage at diagnosis between ALM and CMM may account for a large part of the survival differences. Interestingly, when controlled for thickness, ALM 10-year survival rates for tumors thinner than 1.00 mm and those 2.00 to 4.00 mm thick were still roughly 10% to 20% lower than for CMM overall. When controlled for stage, ALM 10-year survival rates for tumors at stages II and III were 10% to 15% lower than for CMM overall. The lower survival rates seen in ALM may be secondary to reported different biological characteristics of the melanoma subtypes. It has been suggested that there are different genetic pathways in the development of melanoma. Acral lentiginous melanomas have been reported to have significantly lower frequencies of BRAF mutations, which are often found in melanomas from intermittent sun exposure (ie, SSM or NM). Furthermore, one study suggested that ALMs are unique in that they have constitutive activation of the phosphatidyl inositol 3 kinase signaling pathway. Another suggested that ALMs are characterized by focused gene amplifications occurring early in tumorigenesis, and that malignant cells are present beyond the histologically detectable boundary, thereby revealing one mechanism of local recurrence. Although these differences specific to ALM have been reported, they may not necessarily translate into survival differences; hence, the exact cause remains unknown.

Sex differences were also present in the distribution of ALM thickness and stage. Women had significantly higher percentages of stage I and thin melanomas (P < .001), whereas men had higher percentages of stage III and thick melanomas. The distribution of tumor stage and thickness may also explain survival differences in men and women, because women have statistically significantly higher survival rates than men (P < .001). When we adjusted for thickness or stage, there were no differences in survival rates between men and women. Similarly, male patients with CMM overall have also been shown to have poorer survival rates relative to female patients in other studies, with increased tumor thickness at diagnosis being implicated as a causal factor.

Non-Hispanic whites had the highest percentage of thin and stage I ALM, whereas Asian/Pacific Islanders had the highest percentage of stage III and thick (>4.00 mm) ALM tumors. Hispanic whites also had high percentages of stage III tumors. This distribution of ALM tumors may partly explain survival discrepancies among the different racial groups because Asian/Pacific Islanders and His-
panic whites also had the lowest survival rates. These results are consistent with previous results by Cormier et al., who showed that minority populations had lower melanoma survival rates secondary to advanced stage presentation. When controlled for thickness or stage, there were no statistical differences between 5- and 10-year melanoma-specific survival rates in the different racial groups. These results are similar to previous studies that showed, after controlling for stage, similar survival rates among different racial groups with ALM.12,24,37,38

Our study had several limitations. Approximately 50% of the melanoma cases in the SEER database were classified histologically as NOS and therefore excluded from the analyses. Reporting of melanomas as NOS has been a common data limitation in SEER-based analyses.39 Exclusion of the NOS melanomas, however, had no effect on the results. Furthermore, 74 tumors coded as ALMs were reported to be located in anatomic sites other than the upper limbs and lower limbs. These tumors were excluded from the analyses, given their inconsistency with the definition of ALM. In addition, data were extremely limited for AJCC staging for ALM, with only about 60% of cases available for stage analyses. Finally, we used SEER data for this study. We had no information on patients’ socioeconomic status and access to health care, and therefore we were unable to examine these issues in the current study. These factors have been shown to be important for evaluating disparities in cancer survival and health care overall for minorities.12,13

We have shown that ALM has specific epidemiologic characteristics that differ from other types of melanoma. It occurs later in life and on specific palmoplantar locations unattributable to sunlight, unlike other melanoma subtypes.9 Population-based data also showed that the incidence of ALM is similar in non-Hispanic whites and blacks. Hispanic whites have higher incidence rates of ALM, whereas Asian/Pacific Islanders had lower incidence rates. Acral lentiginous melanoma is a frequent melanoma histologic subtype in people of color, with blacks having the highest percentage. Population-based data also showed that ALM is associated with a worse prognosis than CMM overall. The thickness and stage of ALM correlated with survival in sex and the 4 racial groups evaluated. Asian/Pacific Islanders and Hispanic whites had lower survival rates than other groups, and factors such as increased tumor thickness and more advanced stage at presentation are the most likely explanations. The reasons for delayed diagnosis require future study. Even though ALM is rare, given its atypical locations and poor survival rates, it is important that physicians maintain a high index of suspicion in all ethnic groups and closely examine a patient’s palms, soles, and nail beds.

CONCLUSIONS

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Correspondence: Forcia T. Bradford, MD, Genetic Epidemiology Branch, DCEG, NCI, NIH, 6120 Executive Blvd, Room 7003, Rockville, MD 20852-7236 (bradfordp@mail.nih.gov).

Author Contributions: Study concept and design: Bradford and Goldstein. Acquisition of data: Bradford and McMaster. Analysis and interpretation of data: Bradford, Goldstein, McMaster, and Tucker. Drafting of the manuscript: Bradford. Critical revision of the manuscript for important intellectual content: Bradford, Goldstein, McMaster, and Tucker. Statistical analysis: Bradford and Goldstein. Obtained funding: Tucker. Administrative, technical, and material support: Tucker. Study supervision: Goldstein and Tucker.

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