# Using Body Mass Index to Predict Optimal Thyroid Dosing after Thyroidectomy

Kristin A Ojomo, PA, David F Schneider, MD, MS, Alexandra E Reiher, MD, Ngan Lai, BA, Sarah Schaefer, NP, Herbert Chen, MD, FACS, Rebecca S Sippel, MD, FACS

**BACKGROUND:** Current postoperative thyroid replacement dosing is weight based, with adjustments made after thyroid-stimulating hormone values. This method can lead to considerable delays in achieving euthyroidism and often fails to accurately dose over- and underweight patients. Our aim was to develop an accurate dosing method that uses patient body mass index (BMI) data.

**STUDY DESIGN:** A retrospective review of a prospectively collected thyroid database was performed. We selected adult patients undergoing thyroidectomy, with benign pathology, who achieved euthyroidism on thyroid hormone supplementation. Body mass index and euthyroid dose were plotted and regression was used to fit curves to the data. Statistical analysis was performed using STATA 10.1 software (Stata Corp).

**RESULTS:** One hundred twenty-two patients met inclusion criteria. At initial follow-up, only 39 patients were euthyroid (32%). Fifty-three percent of patients with BMI >30 kg/m$^2$ were overdosed, and 46% of patients with BMI <25 kg/m$^2$ were underdosed. The line of best fit demonstrated an overall quadratic relationship between BMI and euthyroid dose. A linear relationship best described the data up to a BMI of 50. Beyond that, the line approached 1.1 μg/kg. A regression equation was derived for calculating initial levothyroxine dose (μg/kg/d = $-0.018 \times$ BMI + 2.13 [$F$ statistic = 52.7, root mean square error of 0.24]).

**CONCLUSIONS:** The current standard of weight-based thyroid replacement fails to appropriately dose underweight and overweight patients. Body mass index can be used to more accurately dose thyroid hormone using a simple formula. (J Am Coll Surg 2013;216:454–460. © 2013 by the American College of Surgeons)

After total thyroidectomy, optimal replacement of thyroid hormone is imperative, but is often challenging to achieve. Suppressive doses of levothyroxine (LT4) increase the risks of accelerated bone loss, fractures, arrhythmias, and decreased left ventricular function.[1-4] Prolonged periods of undertreatment are associated with the clinical features of hypothyroidism, weight gain, dyslipidemia, and cardiovascular dysfunction.[5-7] Both overtreatment and undertreatment are sources of dissatisfaction for patients and a potential source of increased health care costs due to the increased frequency of laboratory testing and physician visits.[8]

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From the Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, Madison, WI (Ojomo, Schneider, Lai, Schaefer, Chen, Sippel) and Division of Endocrinology, Department of Internal Medicine, Northshore University Healthcare System, Evanston, IL (Reiher).

Correspondence address: Rebecca S Sippel, MD, FACS, Section of Endocrine Surgery, Department of Surgery, University of Wisconsin, Clinical Science Center J4/703, 600 Highland Ave, Madison, WI 53792. email: sippel@surgery.wisc.edu

The majority of recommendations on thyroid hormone therapy originate from literature on primary hypothyroidism and are applied to the surgically induced hypothyroid patients.[5,9-13] In primary hypothyroidism, residual thyroid tissue can produce endogenous thyroid hormone, complicating the true requirement of exogenous thyroxine. Studies examining the surgically induced hypothyroid patients are ideal to accurately assess thyroid hormone replacement in this subset. Common practice for initial dosing of LT4 is weight based, with a recommended range of 1.6 to 1.7 μg/kg/d, with certain reports advocating up to 2.1 μg/kg.[9-13] Dose adjustments are subsequently made after serial thyroid-stimulating hormone (TSH) concentrations and clinical evaluation. Goal TSH levels are dependent on pathology. In thyroid cancer, TSH suppression is preferred as adjuvant treatment to reduce tumor reoccurrence.[14] This study focuses on patients with benign thyroid disease whose goal is achieving a TSH value in the normal range.

According to the surgical literature, the time to achieve euthyroidism after thyroidectomy is highly variable, ranging from 2 weeks to 2.5 years, with a median of 3.6





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**Abbreviations and Acronyms**
BMI = body mass index
LBM = lean body mass
LT4 = levothyroxine
TSH = thyroid-stimulating hormone
WBD = weight-based dosing

months.[15] Postoperatively, many patients require multiple dose adjustments before achieving euthyroidism.[15] The conventional method of thyroid replacement therapy involved an empiric dose of 100 to 150 μg/d. After this regimen, between 21% and 37% of patients attained a euthyroid state at initial follow-up.[15,16] The generation of sensitive TSH immunoassays allowed serial titrations of LT4 contingent on TSH values, making weight-based dosing (WBD) more feasible.[17] Unfortunately, widely practiced WBD for initial thyroid hormone replacement has not improved predictability of actual euthyroid dose.[16,18] Sukumar and colleagues[19] compared the empiric dosing method with WBD and found the latter to require considerably more visits before reaching goal TSH levels.

Multiple variables affecting LT4 requirements have been evaluated, including age, sex, body weight, lean body mass (LBM), ideal body weight, body surface area, menopausal state, hormonal status, and pathology.[18,20-24] In addition, co-ingestion of calcium supplements, ferrous sulfate, proton pump inhibitors, bile acid sequestrants, and sucralfate can modify LT4 absorption and complicate postoperative dosing.[25-28]

A few studies suggest LBM predicts LT4 requirement in both surgically induced and primary hypothyroid patients.[23,24] However, more recent literature has shown no superior predictive value of LBM compared with actual body weight.[15,19] From a practical standpoint, an accurate calculation of LBM requires complicated techniques that are impractical in the clinical setting. Research using ideal body weight has disclosed inconsistent outcomes.[18,20] Despite the variability of ideal body weight and LBM, an inverse relationship between LT4 dose per kilogram and overall body weight has been demonstrated consistently.[15,16,19] Lighter patients require a higher LT4 dose per kilogram compared with heavier patients.[15,16] Body surface area has also been strongly correlated with thyroxine requirement.[19] Therefore, it is reasonable to hypothesize that BMI, given its inclusion of both height and weight, might be a superior predictive factor of initial thyroid hormone replacement after total thyroidectomy.

Literature on thyroid hormone replacement in surgically induced hypothyroidism remains scarce, and lacks a single predictive factor with a strong correlation to accurately dose LT4 after surgery. The purpose of this study was to develop a simple algorithm incorporating BMI to improve predictability of initial LT4 dose.

## METHODS

A retrospective review of a prospectively collected thyroid database was performed, and data were abstracted between January 2008 and December 2010. Inclusion criteria were patients who underwent a total thyroidectomy for benign disease, followed up at 6 to 8 weeks for postoperative TSH measurement, and reached normal thyroid function after surgery. Thyroid cancer patients were not included because of the higher dose required to achieve their goal of a suppressed TSH. Excluded were those younger than 18 years old, patients pregnant within 1 year after surgery, those who received T3 supplementation or desiccated thyroid hormone preparations, and gastric bypass patients. A total of 146 patients met criteria and were included in this study. Twenty-four patients were then excluded for not achieving euthyroidism for reasons including irregular follow-up visits, transfer back to home facility, and patient noncompliance with medications. Variables collected included age, autoimmune disease, BMI, and estrogen use. Height and weight were objectively measured at the preoperative clinic visit before surgery and used to calculate BMI.

Before surgery, patients were given verbal instructions about proper administration of LT4. Patients were instructed to take LT4 on an empty stomach, to wait 30 minutes before eating, and to separate their thyroid hormone from calcium, vitamins, or iron supplementation by 4 hours; and to take LT4 at the same time every day. Total thyroidectomy was performed by one of two endocrine surgeons at our institution. Thyroid hormone replacement was initiated on postoperative day 1, with a recommended dose of 1.6 μg/kg/d based on actual body weight. All patients were prescribed brand-name thyroid hormone unless the cost was prohibitive due to lack of insurance coverage. All patients were maintained on the same LT4 preparation they were initiated on to avoid brand switches as a confounding factor.

Patients were seen at a 6- to 8-week postoperative visit, during which TSH values were obtained and dose adjustments were made by the surgeon accordingly. The primary end point was achievement of euthyroidism; defined as a serum TSH level of 0.45 to 4.50 uIU/mL. Either our endocrine surgery nurse practioner or an endocrinologist followed those patients over- or underdosed after the initial visit every 6 to 8 weeks with serial TSH measurements and dose titration. The time to achieve euthyroidism was defined as the time from their surgery to the first normal TSH value.

### Statistical analysis

Multivariate logistic regression was performed to identify the relative impact of age, autoimmune disease, BMI, and estrogen use as predictors of failure to achieve euthyroid at initial 6- to 8-week visit. Sex was excluded due to lack of male patients to provide accurate predictive ability.

Binary comparisons were performed with Student's *t*-test and Pearson chi-square test where appropriate. Comparisons of multiple groups were carried out by ANOVA. Euthyroid dose and BMI were plotted and a quadratic equation was used to determine the limit on BMI. Next, a line of best fit was used to derive a formula from the linear portion of the curve. Patients with a BMI >50 were excluded. Statistical analysis was performed using STATA 10.1 software (Stata Corp). Results are expressed as mean ± SEM. A p value <0.05 was considered significant.

## RESULTS

### Patient characteristics

One hundred and twenty-two patients met inclusion criteria for benign thyroid disease. Pathology comprised benign, multinodular goiter, adenoma, Hashimoto thyroiditis, Graves disease, and hyperplasia (Table 1). Fifty patients had autoimmune disease (Graves disease or Hashimoto thyroiditis). Study participants included 21 men and 101 women. Our study group ranged in age from 18 to 75.6 years, with a mean age of 49.0 years. Before surgery, mean weight was 84.5 kg (range 44.9 to 200.9 kg) and mean height of 1.7 m (range 1.49 to 1.88 m). Body mass index followed a Gaussian distribution, with a mean of 30.5 (range 15.1 to 71.5). Mean initial dose of LT4 after total thyroidectomy was 1.58 μg/kg/d. Median follow-up duration was 4 months, but this was highly variable, as patients were followed until they were euthyroid (range 2 to 29 months).

**Table 1.** Baseline Characteristics and Statistics of Study Participants (n = 122)

| Characteristic | n (%) |
|---|---|
| Sex, n (%) | |
| Women | 101 (82.8) |
| Men | 21 (17.2) |
| Pathology, n (%) | |
| Benign | 10 (8.2) |
| Multinodular goiter | 48 (39.3) |
| Adenoma | 11 (9.0) |
| Hashimoto thyroiditis | 28 (23.0) |
| Graves disease | 22 (18.0) |
| Hyperplasia | 3 (2.5) |
| Descriptive statistics, mean ± SEM | |
| Age, y | 49.0 ± 1.2 |
| Height, m | 1.7 ± 0.007 |
| BMI | 30.5 ± 0.8 |
| Initial dose of LT4,* μg/kg/d | 1.58 ± 0.02 |

*After weight-based dosing regimen of 1.6 μg/kg/d.
BMI, body mass index (calculated as weight in kilograms divided by the square of the height in meters); LT4, levothyroxine.

### Status at 6 to 8 weeks postoperatively

At initial 6- to 8-week postoperative visit, 39 patients were euthyroid (32%), 32 were underdosed (26.2%), and 51 were overdosed (41.8%, Table 2). In comparing patients who achieved euthyroidism at 6 to 8 weeks with those who did not, age and sex were not significantly different (p = 0.93 and p = 0.71, respectively). Additionally, there was no significant difference in initial dosing between those that achieved euthyroidism and those that did not (p = 0.34). Patients who were initially overtreated tended to be older than patients who were initially undertreated; however, this did not reach significance (p = 0.06). Mean BMI in those overdosed was significantly higher compared with underdosed patients (32.3 kg/m$^2$ and 27.0 kg/m$^2$, respectively; p = 0. 018). In other words, patients with a lower BMI tended to be underdosed, and those with a higher BMI were more often overdosed (Fig. 1). In addition, persons with a BMI <25.0 kg/m$^2$ were significantly associated with under-replacement of LT4 (Fig. 1; p = 0.001). Body mass index was significantly different between those patients that achieved euthyroidism and those that did not (Table 2; p = 0.030).

**Table 2.** Status at 6- to 8-Week Postoperative Follow-up

| | | TSH (uIU/mL) | | | |
|---|---|---|---|---|---|
| Variables | All | Overdosed (<0.45) | Euthyroid (0.45–4.5) | Underdosed (>4.5) | p Value |
| n (%) | 122 | 51 (41.80) | 39 (31.96) | 32 (26.23) | |
| Age, y, mean ± SEM | 49.0 ± 1.2 | 51.3 ± 1.8 | 48.8 ± 2.2 | 45.5 ± 2.6 | 0.19 |
| BMI, mean ± SEM | 30.5 ± 0.8 | 32.3 ± 1.5 | 31.0 ± 1.2 | 27.0 ± 1.5 | 0.030 |
| Initial dose of LT4, μg/kg/d, mean ± SEM | 1.58 ± 0.02 | 1.61 ± 0.03 | 1.58 ± 0.05 | 1.53 ± 0.03 | 0.34 |
| Eventual euthyroid dose of LT4, μg/kg/d, mean ± SEM | 1.61 ± 0.03 | 1.46 ± 0.03 | 1.58 ± 0.05 | 1.89 ± 0.07 | <0.0001 |

Differences among groups analyzed with ANOVA.
BMI, body mass index (calculated as weight in kilograms divided by the square of the height in meters); LT4, levothyroxine; TSH, thyroid-stimulating hormone.

The incidence of autoimmune disease also did not differ between those with normal and abnormal TSH values ($p = 0.69$).

### Achievement of euthyroidism

Of the 83 patients who did not achieve euthyroidism at initial postoperative visit, the mean time to achieve normal thyroid function was 7.5 months. At 1 year, 107 (87.8%) patients had achieved a euthyroid state. The mean euthyroid dose was 1.61 ± 0.03 μg/kg/d; however, this euthyroid dose was significantly different between those that were overdosed, underdosed, and euthyroid at initial follow-up (Table 2; $p < 0.0001$). Those with a BMI <30 kg/m$^2$ required a significantly higher dose per kilogram to achieve euthyroidism compared with patients with a BMI >30 kg/m$^2$ (Table 3; $p < 0.001$). Table 3 demonstrates a trend acutely observed in this study that as BMI increases, the dose per kilogram required to achieve euthyroidism decreases.

Sex did not influence the dose of LT4 needed to achieve euthyroidism ($p = 0.41$). In patients with either Hashimoto thyroiditis or Graves disease, a statistically greater dose was required compared with those without autoimmune disease ($p = 0.03$).

### Multivariate analysis

On multivariate analysis, BMI was the only significant factor predicting achievement of euthyroid dose at initial postoperative visit. Analysis indicated patient age, autoimmune disease, and estrogen use did not independently influence achievement of normal TSH values (Table 4). For those patients older than age 50, with a BMI >25 kg/m$^2$, more than half were initially overdosed and required adjustments, and only one third achieved euthyroidism on initial dose. Those in the group older than age 50 with a BMI <25 kg/m$^2$ were predominately underdosed, supporting a relationship between BMI and euthyroid dose independent of age.

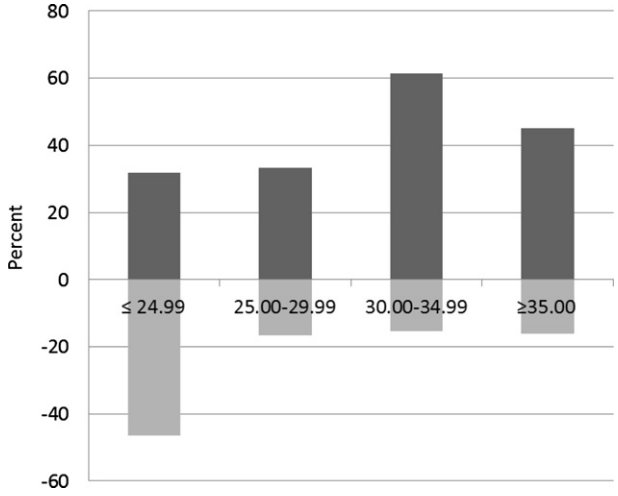


**Figure 1.** Distributions of patients not euthyroid at initial 6- to 8-week follow-up, by body mass index (calculated as weight in kilograms divided by the square of the height in meters) category. Dark gray, overdosed; light gray, underdosed.

**Table 3.** Eventual Euthyroid Dose of Levothyroxine by Body Mass Index Category

| BMI | n | Mean euthyroid dose, μg/kg/d, mean ± SEM |
|---|---|---|
| ≤24.99 | 41 | 1.84 ± 0.07 |
| 25.00–29.99 | 24 | 1.63 ± 0.05 |
| 30.00–34.99 | 26 | 1.50 ± 0.05 |
| ≥35.00 | 31 | 1.39 ± 0.05 |
| | | $p \leq 0.001$ |

Differences among groups analyzed with ANOVA.
BMI, body mass index (calculated as weight in kilograms divided by the square of the height in meters).

### Development of body mass index–based formula for postoperative thyroxine dosing

After the multivariate analysis results, euthyroid dose and BMI were plotted. Regression analysis demonstrated an overall quadratic relationship between euthyroid dose and BMI, but the curve appeared linear up to a BMI of 50 kg/m$^2$, and beyond that, approached 1.1 μg/kg (Fig. 2). As BMI increased, euthyroid dose per kilogram decreased. There were 6 patients with a BMI >50 kg/m$^2$. A dosing algorithm for patients with a BMI <50 kg/m$^2$ was computed using linear regression for the linear portion of the curve (Fig. 3).

## DISCUSSION

Our study reinforces current literature that a purely WBD method fails to accurately and efficiently predict thyroid hormone replacement in the surgically induced hypothyroid population. In our study, only 32% of patient's achieved euthyroidism at initial follow-up. A similar study by Jonklaas[18] evaluated the effectiveness of WBD after total thyroidectomy for benign thyroid disease and thyroid

**Table 4.** Multivariate Analysis of Factors Affecting Euthyroid Failure of Initial Levothyroxine Dose Postoperatively

| Parameter | p Value |
|---|---|
| Age | 0.215 |
| Autoimmune disease | 0.110 |
| BMI | 0.008 |
| Estrogen use | 0.309 |

BMI, body mass index (calculated as weight in kilograms divided by the square of the height in meters).

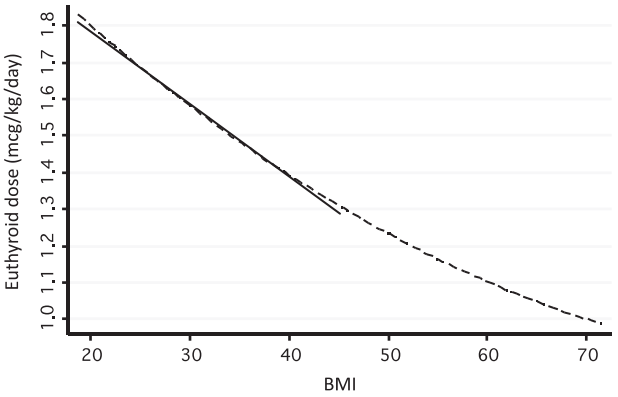


**Figure 2.** Regression analysis. Solid line, linear regression; dashed line, quadratic regression. BMI, body mass index (calculated as weight in kilograms divided by the square of the height in meters).

cancer. At 6- to 8-week follow-up, 32% of patients were at goal and by 1 year, 90% were adequately replaced.[18] In our study, 87.8% of patients were euthyroid at 1 year.

Mistry and colleagues[16] compared 3 different dosing methods in patients undergoing total thyroidectomy. After the WBD method, 25% of patients were correctly replaced on their initial dose.[16] The empiric dosing method was inferior, with 21% of patients euthyroid at follow-up. Their proposed dosing method, a derived regression equation including weight and age, correctly dosed only 28% of patients.[16]

The relationship observed between BMI and euthyroid dose predictability is the most noteworthy finding of our study. Our results substantiate tendencies to overdose patients who are overweight and underdose patients of normal BMI after a WBD regimen. This result is physiologically intuitive, as fat cells function primarily as energy storage as opposed to expenditure.[29] It would therefore be expected that overweight individuals require less dose per kilogram of thyroid replacement and might be at risk of oversupplementation after WBD. In this study, the mean dose per kilogram that adequately replaced thyroxine decreased with increasing BMI.

In addition, this phenomenon has substantial implications when compared with studies on anorexia nervosa, obesity, and thyroid function. Anorexia nervosa is associated with both low TSH and lower levels of T3, understood to be an adaptive process for preserving resting energy potential.[30,31] The low T3 levels are attributed to an impaired ability to convert T4 to T3 in the periphery.[30,32,33] The opposite is demonstrated in the obese population. Compared with patients of normal weight, obese patients have slightly increased TSH and free T3 levels and produce a greater ratio of free T3 to reverse T3.[30,34-36] When obese patients receive LT4 postoperatively, their ability to convert more thyroxine to T3 might explain the lower ideal dose per kilogram of LT4 observed in our study. Although our patients are not in a starving state, the higher thyroxine dose per kilogram in lower BMI patients might be due an impairment of T4 conversion.[30,32,33]

Mcg/kg/day= -.018*BMI +2.13

**Figure 3.** Dosing algorithm for levothyroxine postoperatively in those patients with a body mass index (BMI; calculated as weight in kilograms divided by the square of the height in meters) <50. $F = 52.7$, root mean square error of 0.24.

Although the increased prevalence of thyroid disease among older women is well known, age as a predictor for LT4 dosing is debated.[16,18,20, 21,37] Studies on primary hypothyroidism conclude that LT4 requirements decrease with age due to a slowing rate of thyroxine degradation.[3,13,38] A recent retrospective review compared male patients with pre- and postmenopausal women and found age-based differences could be accredited instead to changes in body weight, body composition, or hormonal status in women.[21] Likewise, our multivariate analysis did not find age to be a predictive factor for initial euthyroid dose.

Certain medications consumed concurrently with LT4 can affect the therapeutic requirement. Patients on both LT4 and estrogen show an estrogen-induced increase in thyroxine binding concentration, slightly lowering the amount of free thyroxine available.[22] Clinically, close follow-up of TSH levels is recommended in these patients to make appropriate dose adjustments as needed.[22] Our multivariate analysis did not find estrogen use to be an independent factor of failure to achieve euthyroidism.

The pathology of hypothyroidism can also influence the required dose of thyroid hormone. In Hashimoto thyroiditis and Graves disease, if thyroid tissue remains, persistent endogenous production of thyroxine can effect LT4 requirements.[10] In this study, we included only patients who underwent total thyroidectomy to control for this factor. Autoimmune diseases were included in our analysis to assess if the pathology itself, regardless of residual tissue, affected the patient's ability to become euthyroid after surgery. Surprisingly, we found a substantially greater dose of LT4 required to achieve euthyroidism in patients with autoimmune disease, suggesting a persistent role of immune activity influencing thyroxine replacement, despite complete removal of thyroid tissue. The cause of this is unclear and understudied, but might be due to circulating antibodies or altered metabolism.

Several factors limited this analysis. There was some variation in starting dose, as not all of our patients were

initiated on exactly 1.6 μg/kg/dose (Table 2). Due to insurance coverage, not all of our patients received the same preparation of LT4, which might have influenced efficacy and achievement of euthyroidism. Second, the retrospective nature of our study did not allow us to account whether patients were taking medications that affect LT4 dosing, or whether patients had malabsorptive issues or cardiac disease, all of which can result in suboptimal dosing. After a thyroidectomy at our institution, patients are placed on calcium, which raises concern about interference with LT4 absorption. All patients were treated with standard protocol of calcium supplementation after thyroidectomy, and given instructions on proper administration of calcium, so this should limit the extent of this bias. In addition, calcium supplementation was stopped in almost all patients at 2-week follow-up.

The importance of strict adherence to daily thyroxine supplementation was communicated, however, patient compliance might also have affected the delay in achieving euthyroidism. Patients were given thorough instructions on how to properly take thyroid hormone and warned of the effect of food and supplements on the absorption rate.

Although the overall fit for the proposed algorithm is not perfect, the results of this study clearly emphasize the role of BMI in determining a postoperative dosing regimen. A follow-up study at our institution is currently underway to investigate prospectively the use of the proposed algorithm and its efficacy.

## CONCLUSIONS

Despite these limitations, our study reaffirms that WBD regimen insufficiently predicts thyroxine requirements postoperatively. We propose BMI as a predictive factor and suggest its use in a clinically simple equation can better predict LT4 dosing and shorten the time to achieving euthyroidism.

### Author Contributions

Study conception and design: Schneider, Reiher, Schaefer, Chen, Sippel

Acquisition of data: Ojomo, Lai

Analysis and interpretation of data: Ojomo, Schneider, Reiher, Lai, Sippel

Drafting of manuscript: Ojomo, Schneider, Reiher, Sippel

Critical revision: Schneider, Schaefer, Chen, Sippel

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