INTRODUCTION

Food allergy (FA) is a major public health concern, particularly in children and adolescents, with prevalence increasing globally. Poor treatment options and fear of accidental exposure can negatively impact food allergy health–related quality of life (FAQL) for the child/adolescent and caregiver. This includes significant negative impacts across several health-related quality-of-life (HRQL) domains, including physical, social, emotional, and psychosocial health.

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Original Article

Deriving health utility indices from a food allergy quality-of-life questionnaire

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Abstract

Background: The Food Allergy Quality-of-Life Questionnaire-Parent Form (FAQLQ-PF) is widely used to assess food allergy–specific health-related quality of life (FAQL), but cannot be used directly in cost-utility analyses, which require health state utility (HSU) scores. Currently, limited evidence is available regarding the HSU of food-allergic children/adolescents. This study aimed to develop mapping algorithms from the FAQLQ-PF onto HSU scores generated by generic, preference-based, health-related quality-of-life (HRQL) instruments.

Methods: Caregivers of children aged 7 to 17 years with a clinician diagnosis of IgE-mediated food allergy, recruited via Allergy & Anaphylaxis Australia, completed an online FAQLQ-PF questionnaire and proxy generic preference-based pediatric instruments (Assessment of Quality of Life [AQoL]-6D and Child Health Utility 9D [CHU9D]). Optimal statistical methods were based on series of goodness-of-fit statistics.

Results: Mean FAQLQ-PF total score, AQoL-6D, and CHU9D utility scores of 238 food-allergic children/adolescents were 3.49 (SD: 1.41), 0.78 (SD: 0.22), and 0.74 (SD: 0.22), respectively. The Spearman correlation coefficients of FAQLQ-PF with AQoL-6D and CHU9D were rho = −0.56 and rho = −0.45, respectively. Optimal mapping algorithms were generated from selected FAQLQ-PF items, mapped onto AQoL-6D or CHU9D utility scores, with AQoL-6D demonstrating better performance.

Conclusions: This study generated mapping algorithms to help facilitate the use of FAQLQ-PF for cost-utility analyses, which are essential for health economic evaluation. External validation of the reported mapping algorithms is warranted.

Keywords
food allergy, health state utility, mapping, quality of life, quality-adjusted life years

1 INTRODUCTION

Food allergy (FA) is a major public health concern, particularly in children and adolescents, with prevalence increasing globally. Poor treatment options and fear of accidental exposure can negatively impact food allergy health–related quality of life (FAQL) for the child/adolescent and caregiver. This includes significant negative impacts across several health-related quality-of-life (HRQL) domains, including physical, social, emotional, and psychosocial health.
HRQL measures can be categorized as either non–preference-based or preference-based instruments. Preference-based HRQL instruments can be used to elicit health state utility (HSU) scores that take into account the preference on different health states by the general population and lie on a 0 to 1 (death to full health) quality-adjusted life-years (QALYs) scale. The QALYs, which incorporate quality (ie, HSU) and quantity of life into a single measure, are commonly used as outcomes in cost-utility analyses (CUAs), which is a form of cost-effectiveness analysis that compares interventions in terms of cost per unit of effect.6,7 Current food allergy-specific HRQL instruments such as the Food Allergy Quality-of-Life Questionnaire-Parental Form (FAQLQ-PF) series are all non–preference-based, and therefore, transformation is needed to derive a health utility score so that they can be used for health economic evaluation.

As new food allergy treatment/management options become available, understanding their cost-effectiveness is crucial to their valuation process, given the limited healthcare resources available.6,8-10 Among different types of economic evaluation methods, CUA is widely preferred by regulatory authorities and healthcare agencies globally, such as the National Institute for Health and Care Excellence (NICE) and Pharmaceutical Benefits Advisory Committee (PBAC) in Australia.11 Recent work suggests that peanut oral and epicutaneous immunotherapies can be cost-effective under certain contexts, but are critically dependent on HSU improvements.8 Most immunotherapy clinical trials to date have used non–preference-based HRQL measurement and have shown that FAQL does improve due to treatment. However, the findings are not translatable to QALY change, and models have therefore had to rely on HSU estimates indirectly derived from HRQL literature, which may not accurately reflect the HSU of participants in the trial and lead to a bias in economic evaluation.

Mapping (or “crosswalk”) is a widely used approach to develop transformational algorithms that can be used to predict HSU from non–preference-based HRQL instruments.12 The mapping algorithms can be used to facilitate conducting CUAs of health technologies when a preference-based HRQL is not included in clinical trials.13 Although most mapping studies have focused on preference-based instruments in adults, there is growing literature on mapping algorithms developed for pediatric preference–based instruments.14-17

The FAQLQ-PF is a widely used validated, food allergy–specific, non–preference-based instrument to assess parents’ perception of food allergy HRQL in children.18-20 However, it was not developed as a preference-based instrument and does not measure HSU. The study aimed to map the FAQLQ-PF to generic preference-based HRQL instruments to allow the prediction of HSU from the FAQLQ-PF.

2 | METHODS

2.1 | Study Design

A voluntary and anonymous cross-sectional survey was conducted from October to December 2019. Participants were caregivers of children aged 7 to 17 years with a self-reported clinician diagnosis of IgE-mediated food allergy, recruited via advertising on the Allergy & Anaphylaxis Australia (A&AA) website, on its Facebook page, and by distribution to A&AA members. A&AA is the pre- eminent patient and caregiver food allergy advocacy and support group in Australia. Published literature on mapping studies suggests that a sample size of approximately 100 to 200 is sufficient for deriving mapping algorithms; thus, we aimed for a sample size of approximately 200 caregivers in this study.12,21

The online survey was completed by caregivers and consisted of three main sections. First, caregivers provided demographic information, confirmation that the food allergy was physician-diagnosed, and food allergy background and history of their food-allergic child. Next, the FAQLQ-PF and two generic pediatric-specific preference-based HRQL instruments were administrated. Respondents provided consent online prior to the completion of the survey. The study was approved by the Sydney Children’s Hospitals Network Human Research Ethics Committee (SCHN-HREC Reference: 2019/ETH00677) and conformed to the principles outlined in the Declaration of Helsinki.

2.2 | HRQL Measures

2.2.1 | Non–preference-based instrument

The FAQLQ-PF is a caregiver proxy-report measure for a child. Using a proxy report ensured that assessment could be undertaken for children across a wider age range and allowed for recruitment of parents via the Internet, which would not have been an acceptable or feasible way to recruit young children, using the FAQLQ-Child Form. The FAQLQ-PF has 30 items with a 7-point response scale (from 0 = no impact on HRQL to 6 = extreme impact on HRQL) with higher scores indicating more HRQL impairment. Items may be grouped into three subscales: general emotional impact (13 items), food-related anxiety (8 items), and social and dietary limitations (9 items). The total score is calculated as the mean of the three subscales.18 To facilitate

Key Message

Food Allergy Quality-of-Life Questionnaire-Parental Form (FAQLQ-PF) is one of the most widely used food allergy-specific instruments for assessing the psychosocial impacts of the disease. This study developed mapping algorithms that can predict the health utility score from FAQLQ-PF. Outputs from this study can facilitate health economic evaluation for food allergy–related interventions. This is the first mapping study been conducted among children with food allergy. The developed mapping algorithms can be used to predict health state utility scores for conducting cost-utility analyses whenever FAQLQ-PF data are available.
more age-tailored approaches, the 30 items have been grouped into 3 sections (A, B, and C), with Section A for children aged 0–3 years, Sections A and B for children aged 4–6 years, and all three sections for children aged ≥7 years.

### 2.2.2 Generic preference-based instruments

The Assessment of Quality of Life (AQLQ)-6D and the Child Health Utility 9D (CHU9D) are two validated, generic, preference-based pediatric HRQL instruments, which assess general health state utility. The AQLQ-6D has 20 items with either a 4- or a 6-point response scale (a higher level = more severe impairments). The items are grouped into six dimensions: independent living, relationships, mental health, coping, pain, and senses. The CHU9D has nine items, each representing one dimension: worried, sad, pain, tired, annoyed, schoolwork/homework, sleep, daily routine, and ability to join in activities. Each dimension has five response levels (higher levels = more severe impairments). Caregiver proxy versions of these two instruments were used, and both were scored based on their official Australian-specific scoring algorithm (eg, a “value set”) to produce a health utility score (where higher scores indicate better health status).

### 2.3 Statistical Analyses

Descriptive statistics on demographic and food allergy background and HRQL scores of children were reported, as well as Spearman’s correlations between FAQLQ-PF and AQLQ-6D/CHU9D. The FAQLQ-PF items were used as key predictors in a regression framework to explore optimal mapping functions from the FAQLQ (independent variables) onto the AQLQ-6D and CHU9D utilities (dependent variable). The decision not to include other potential predictors will ensure the developed mapping algorithm can be more widely used by other researchers. Stepwise regression with forward selection was used to select the statistically significant (p < .10) predictors to be included in the final mapping functions, with a constant included in all regressions. Initially, all 30 items were considered in stepwise regression, and for CHU9D, it was found that two items from Section C of FAQLQ-PF were significant (for detailed results, see Tables S2 and S3 in Supporting Information II). However, considering that for younger children, questions in Section C are not intended to be answered based on their age, when developing the mapping algorithms for CHU9D, four questions in Section C were not used.

Three main statistical methods that either have been widely adopted in previous literature or can better cope with the non-normal distribution of health utility scores were used to explore optimal mapping functions for FAQLQ-PF items onto CHU9D/AQLQ-6D utilities: ordinary least squares (OLS) estimator, beta regression (BETA), and the generalized linear model (GLM). For mapping onto the CHU9D, the TOBIT model was considered as well because of the observed ceiling effect of CHU9D utility, specifically the large proportion of respondents with a utility of 1 (eg, full health) on the CHU9D health state classification system.

The best-performing mapping algorithms were identified by examining the goodness-of-fit results from the internal 10-fold validation analysis (see Supporting Information I), which included the mean absolute error (MAE; the average of the absolute prediction errors with smaller values reflecting for accurate prediction), the concordance correlation coefficient (CCC; a statistic that quantifies the agreement between observed and predicted utilities, where larger values reflect more accuracy), and the proportion of predicted utilities deviating from observed utilities by absolute error <0.05 (diff < 0.05). The mean, minimum, and maximum of the predicted HSU score, as well as Spearman’s correlations between the predicted and observed HSU scores, are also reported. All statistical analyses were performed using Stata software, version 16.

### 3 RESULTS

#### 3.1 Sample Characteristics

A total of 238 respondents (96% by mothers) completed the survey on behalf of their food-allergic child (mean age 11.4 years) (Table 1). Of these 238 children, 66% were allergic to tree nuts, 65% to peanut, 37% to egg, and 22% to cow’s milk. Among them, 34% reported experiencing anaphylaxis to peanut and 21% had experienced

| TABLE 1 Characteristics of Children With Food Allergy (N = 238) |
|-----------------------------|-----------------------------|
| **Socio-demographic characteristics** | |
| Age, mean (SD) | 11.4 (3.1) |
| Male, n (%) | 141 (59.2) |
| Food allergy background, n (%) | |
| Allergy specialist confirmed | 234 (98.3) |
| Epinephrine auto-injector prescribed | 227 (95.4) |
| Anaphylaxis to peanuts | 81 (34.0) |
| Experienced anaphylaxis to any food in the past 12 months | 50 (21.0) |
| No. of foods child has to avoid | |
| 0–2 | 76 (31.9) |
| 3–6 | 94 (39.5) |
| 7–10 | 27 (11.3) |
| 10+ | 41 (17.2) |
| HRQL, mean (SD) | |
| FAQLQ-PF, total score | 3.49 (1.41) |
| AQLQ-6D utility | 0.78 (0.22) |
| CHU9D utility | 0.74 (0.23) |

Note: Proxy-assessed version was used for all health-related quality-of-life (HRQL) measures.

Abbreviations: AQLQ-6D, Assessment of Quality of Life 6D; CHU9D, Child Health Utility 9D; FAQLQ-PF, Food Allergy Quality-of-Life Questionnaire-Parental Form; SD, standard deviation.
anaphylaxis to any food in the past 12 months. For the mapping sample, the mean total score (SD) on the FAQLQ-PF was 3.49 (1.4), and the mean (SD) utility scores on the AQoL-6D and CHU9D were 0.78 (0.22) and 0.74 (0.23), respectively. A moderate correlation of 0.62 was found between AQoL-6D and CHU9D.

3.2 | Relationship Between FAQLQ-PF and AQoL-6D/CHU9D

The distribution of the scores of three instruments, as well as the scatter plots between FAQLQ-PF and AQoL-6D/CHU9D, is presented in Figure 1. A stronger relationship was found between FAQLQ-PF and AQoL-6D than between FAQLQ-PF and CHU9D; Spearman’s correlation between the FAQLQ-PF total score and AQoL-6D was -0.556 compared with -0.446 for CHU9D. Detailed Spearman’s correlations between FAQLQ-PF and AQoL-6D/CHU9D are shown in Table S1 in Supporting Information II.

3.3 | Development of Mapping Algorithms

The goodness-of-fit statistics are presented in Table 2. Based on the internal (10-fold) validation results, the best two mapping algorithms onto AQoL-6D are based on the OLS and GLM. For CHU9D, the best two mapping algorithms were developed based upon TOBIT and BETA. Optimal algorithms demonstrated good performance in these additional validations. Based on three goodness-of-fit statistics of the optimal mapping functions to AQoL-6D compared with CHU9D in the validation exercise—MAE (0.131 vs. 0.163), CCC (0.556 vs. 0.387), and percentage of |diff| < 0.05 (31% vs. 18%)—mapping FAQLQ-PF to AQoL-6D had better performance than mapping onto CHU9D utility scores.

3.4 | Optimal Mapping Algorithms

Estimated regression coefficients of the optimal mapping functions for the AQoL-6D and CHU9D utility scores are presented in Table 3. Neither age nor gender contributed significantly (both \( p > .1 \)) and was not included in the final mapping algorithms. The \( R^2 \) statistic was substantially larger in the AQoL-6D equation (\( R^2 = 0.415 \)) than in the CHU9D equation (\( R^2 = 0.276 \)).

By using the reported coefficients, the HSU can be predicted from FAQLQ-PF items. For example, using the optimal OLS estimates, the predicted AQoL-6D utility can be calculated as:

\[
{\text{AQoL-6D}}_{\text{Predicted}} = 0.986084 - 0.0334\times {\text{FAQLQ}}_{A6} - 0.019246\times {\text{FAQLQ}}_{B23} - 0.030900\times {\text{FAQLQ}}_{B25}. 
\]

Similarly, CHU9D utility can be predicted from optimal TOBIT estimates:

\[
{\text{CHU9D}}_{\text{Predicted}} = 0.955192 - 0.032753\times {\text{FAQLQ}}_{A6} - 0.016239\times {\text{FAQLQ}}_{A11} - 0.032061\times {\text{FAQLQ}}_{B25}. 
\]

It should be noted that both GLM and BETA regressions are non-linear models and transformation is required during the calculation of the predicted HSUs. All mapping functions reported in Table 3 have been coded as Stata syntax in Supporting Information III, in which the detailed wordings of corresponding items are also included (Table S4).

4 | DISCUSSION

Eliciting health state utility scores from children and adolescents with food allergy is an important step in the evaluation of health and economic outcomes for this population, so that QALY gain/loss can be understood and applied.\(^6,8,9\) However to date, such information is very limited.\(^24\) To our knowledge, this is the first study to map FAQLQ-PF to HSU instruments. Two generic HSU instruments

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**FIGURE 1** Distributions Across the 3 HRQL Instruments and Scatter Plots Between FAQLQ-PF and AQoL-6D/CHU9D. AQoL-6D, Assessment of Quality of Life 6D; CHU9D, Child Health Utility 9D; FAQLQ-PF, Food Allergy Quality-of-Life Questionnaire-Parental Form; HRQL, health-related quality of life.
(AQoL-6D and CHU9D) were evaluated, with AQoL-6D found to have a stronger correlation with FAQLQ-PF. The reported mapping algorithms can be used to calculate HSU for CUAs in clinical trials when the FAQLQ-PF was used.

Our findings are in line with previously published data showing that FAQL is negatively impacted in children with food allergy. In our current cohort, the total mean FAQLQ score was 3.5 (on a 0–6 scale), considered reasonably typical of a food-allergic cohort, with a trend toward higher scores in the older children in a sample broadly representative of the Australian pediatric and adolescent food-allergic population. The mean HSUs are close to the previously reported community adolescents in Australia (comprised of populations with and without chronic disease): a mean score of 0.74 for the CHU9D in this study compared with 0.72 (ages 15–17) and 0.82 (ages 10–12); and 0.78 (ages 11–17) for AQoL-6D.\textsuperscript{15,16,25}

Unique to this study, two preference-based instruments were included in the study design. They were both scored using Australian-specific tariffs developed from adolescents. Although different generic preference-based instruments have been used to measure HSUs, their psychometric properties vary depending on the diseases of interest. In this study, two preference-based instruments were moderately correlated (Spearman’s correlation coefficient of 0.62) and had a comparable mean score.

Mapping to the AQoL-6D outperformed mapping to the CHU9D in terms of \(R^2\) and goodness-of-fit statistics. There are several explanations for the difference in accuracy. The AQOL-6D contains more comprehensive/multidimensional items in the health state classification system, including psychosocial domains related to relationships, mental health, and coping, and although generic in nature, they may better align with the items and subscales of the FAQLQ compared with the CHU9D. However, the findings may also be sample- and/or country-specific.

The choice of which HSU instrument to map may depend on several considerations. For instance, certain government agencies may

| TABLE 2  Goodness-of-Fit Statistics (\(N = 238\)) |
|-----------------------------------------------|
| **Model**                                      |
| **Mean** | **Min** | **Max** | **Correlation** | **CCC** | **MAE** | |diff| < 0.05, (%) |
| Assessment of Quality of Life (AQoL)-6D        |
| Observed                                      | 0.782  | 0.136  | 1          | –   | –   | –   | –   |
| Panel A: full sample                          |
| OLS                                           | 0.782  | 0.485  | 0.986  | 0.658 | 0.587 | 0.126 | 31.090 |
| BETA                                          | 0.775  | 0.465  | 0.920  | 0.660 | 0.551 | 0.131 | 20.170 |
| GLM-1                                         | 0.782  | 0.401  | 0.928  | 0.640 | 0.582 | 0.127 | 24.370 |
| GLM-2                                         | 0.782  | 0.369  | 0.923  | 0.640 | 0.584 | 0.127 | 23.110 |
| Panel B: 10-fold internal validation          |
| OLS                                           | 0.781  | 0.461  | 1.006  | 0.632 | 0.556 | 0.131 | 31.090 |
| BETA                                          | 0.775  | 0.477  | 0.942  | 0.629 | 0.526 | 0.136 | 20.590 |
| GLM-1                                         | 0.784  | 0.405  | 0.950  | 0.605 | 0.549 | 0.132 | 23.950 |
| GLM-2                                         | 0.782  | 0.372  | 0.927  | 0.623 | 0.573 | 0.129 | 23.530 |
| Child Health Utility 9D (CHU9D)                |
| Observed                                      | 0.739  | 0.105  | 1          | –   | –   | –   | –   |
| Panel A: Full Sample                          |
| OLS                                           | 0.739  | 0.488  | 0.909  | 0.528 | 0.430 | 0.156 | 14.710 |
| BETA                                          | 0.765  | 0.337  | 0.971  | 0.539 | 0.474 | 0.155 | 16.390 |
| GLM-1                                         | 0.739  | 0.539  | 0.933  | 0.528 | 0.420 | 0.157 | 15.550 |
| GLM-2                                         | 0.739  | 0.519  | 0.919  | 0.527 | 0.425 | 0.157 | 16.390 |
| TOBIT                                         | 0.755  | 0.469  | 0.955  | 0.517 | 0.456 | 0.155 | 21.430 |
| Panel B: 10-fold internal validation          |
| OLS                                           | 0.739  | 0.496  | 0.918  | 0.477 | 0.385 | 0.162 | 13.450 |
| BETA                                          | 0.761  | 0.353  | 0.969  | 0.411 | 0.392 | 0.168 | 17.650 |
| GLM-1                                         | 0.740  | 0.541  | 0.936  | 0.475 | 0.376 | 0.163 | 13.030 |
| GLM-2                                         | 0.740  | 0.520  | 0.934  | 0.479 | 0.384 | 0.163 | 12.180 |
| TOBIT                                         | 0.756  | 0.480  | 0.996  | 0.446 | 0.387 | 0.163 | 18.490 |

Note: [diff] < 0.05, the proportion of predicted utilities deviating from observed utilities by absolute error <0.05. The best two results are in bold. Abbreviations: BETA, beta regression; CCC, concordance correlation coefficient; For GLM-1, family(binomial) and link(logit) were specified; For GLM-2, family(binomial) and link(log-log) were specified; GLM, generalized linear models; Goodness-of-fit statistics; MAE, mean absolute error; OLS, ordinary least squares regression; TOBIT, Tobit regression.
select a specific instrument. The NICE in the UK recommends EQ-5D be used, whereas the PBAC in Australia does not specify the use of a particular instrument. Other considerations include the existence of country-specific value sets and whether a preference-based instrument was included in a clinical trial. Based on our findings, for Australian populations, mapping to the AQoL-6D should be prioritized over the CHU9D. Studies in other populations are needed to determine whether this performance superiority can be replicated.

We acknowledge some limitations. Although the goodness-of-fit statistics of mapping FAQLQ-PF onto AQoL-6D were comparable to the available published literature on generic-to-generic comparisons (see Supporting Information IV), we noted two key limitations that are commonly documented in mapping studies. First, mapping algorithms tend to underpredict the top distribution and overpredict the bottom distribution of the HSU score. This may lead to an underestimation of the health gain (treatment effect) of an intervention. Second, owing to the nature of a disease-specific instrument, the unique items that are sensitive to disease-specific symptoms or impairments are less likely to be captured by a generic preference-based instrument.

### Table 3

| FAQLQ item# | Mapping onto AQoL−6D | Mapping onto CHU9D |
|-------------|----------------------|-------------------|
|             | OLS                  | GLM               | TOBIT            | BETA |
| A1          | 0.166373             |                   |                  |      |
| A5          | 0.146603             |                   |                  |      |
| A6          | -0.033400 (0.008)**  | -0.203907 (0.092)** | -0.032753 (0.010)** |      |
| A7          |                     | -0.126726 (0.066)* |                  |      |
| A10         | 0.137752 (0.055)**   |                   |                  |      |
| A11         |                     | -0.016239 (0.009)* | -0.277166 (0.076)** |      |
| A13         | 0.109705 (0.051)**   |                   |                  |      |
| A14         | 0.136393 (0.063)**   |                   |                  |      |
| B20         |                     | -0.190825 (0.065)** |                  |      |
| B22         |                     | -0.138417 (0.065)** |                  |      |
| B23         | -0.019246 (0.009)**  |                   |                  |      |
| B25         | -0.030900 (0.008)**  | -0.217251 (0.082)** | -0.032061 (0.009)** | -0.309188 (0.043)** |
| Constant    | 0.986084 (0.021)**   | 2.529292 (0.306)** | 0.955192 (0.030)** | 2.266592 (0.206)** |
| Scale       | 0.964661 (0.094)**   |                   |                  |      |
| Observations| 238                  | 238               | 238              | 238  |
| R-squared   | 0.415                |                   |                  |      |

**Note:** The optimal two mapping functions were reported for Assessment of Quality of Life (AQoL)-6D and Child Health Utility 9D (CHU9D). Standard errors in parentheses. ***p < .01, **p < .05, and *p < .1.

**Abbreviations:** BETA, beta regression; For GLM, family (binomial) and link (log-log) were specified; GLM, generalized linear models; OLS, ordinary least squares regression; TOBIT, Tobit regression.
5 | CONCLUSIONS

Eliciting HSU scores for children and adolescents with food allergy is essential for health economic evaluation. The present mapping study is the first to predict pediatric health utility scores from a food allergy HRQL instrument internationally. Based on our results, mapping of FAQLQ-PF onto AQoL-6D would be preferred to mapping onto CHU9D utility scores; however, both are viable methods. The generated mapping algorithms will facilitate the use of FAQLQ-PF for cost-utility analyses, including the use of historical data from past interventional trials where HSU was not directly measured, with a performance comparable to other disease-specific mapping algorithms.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Gang Chen: Conceptualization (equal); Data curation (lead); Formal analysis (lead); Methodology (lead); Project administration (equal); Software (lead); Writing-original draft (lead). Audrey DunnGalvin: Writing-review & editing (equal). Matthew Greenhawt: Writing-review & editing (equal). Marcus S Shaker: Writing-review & editing (equal). Dianne E Campbell: Conceptualization (equal); Funding acquisition (lead); Project administration (equal); Writing-review & editing (equal).

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.