Supporting diversity and inclusion through the evaluation of differential item functioning (DIF) by race and ethnicity in the Asthma Control Questionnaire – 5 items (ACQ-5) and Asthma Quality of Life Questionnaire (AQLQ) using dupilumab phase 3 study data

ASTHMA

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Introduction

- The Food and Drug Administration (FDA) has stressed the importance of including patients from diverse racial and ethnic backgrounds in clinical trials.[1]
- Differential item functioning (DIF) analysis can be used to examine the extent to which patient-reported outcome (PRO) measures administered in clinical trials support the generalization of their respective endpoint results across diverse populations.
- Global dupilumab clinical trial data of participants with persistent asthma (NCT02414854) were used to examine the presence of DIF on the Asthma Control Questionnaire–5 items (ACQ-5) and Asthma Quality of Life Questionnaire (AQLQ) by race and ethnicity.

Methods

Study Design and Participants

- The study was a phase 3, global, randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma.
- 1902 participants aged 12 years and older were enrolled.

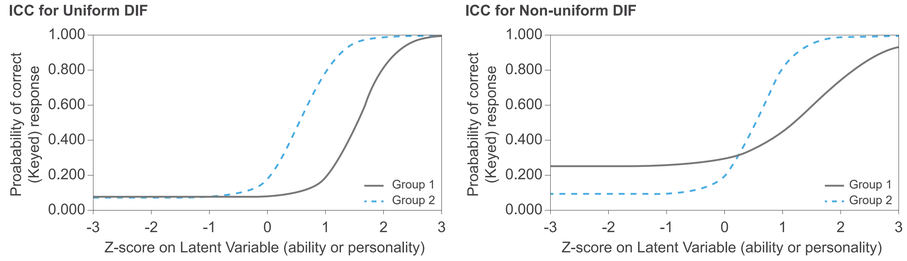
Patient-reported Outcomes

- ACQ-5
  - Includes the first 5 items of 7-item ACQ and measures asthma control.
  - Items assessed on 7-point Likert scale (e.g., not at all to all the time).
  - Recall period: the past week.
  - Higher scores indicate lower asthma control.
- AQLQ
  - 32-item instrument that assesses symptoms, activity limitation, emotional function, and environmental exposure.
  - Items assessed on 7-point Likert scale (e.g., totally limited to not at all limited).
  - Recall period: last two weeks.
  - Higher scores indicate better quality of life.

Statistical Analysis

- DIF analysis using logistic regression was conducted to investigate if respondents with same level of asthma burden had a different probability of endorsing a response on the ACQ-5 and AQLQ between 1) Hispanic and non-Hispanic; 2) Black/African American and White; and 3) Asian and White.
- Graphical representations of these relationships by item (Item Characteristic Curves [ICC]), and overall (Test Characteristic Curves [TCC]) were generated using a hybrid method of logistic regression and item response theory (IRT).[2]
- DIF can be uniform or non-uniform **Figure 1**.[3,4]
- Baseline and post-treatment data (Weeks 24 and 52) were used and DIF effect size (negligible: R^2<0.13; moderate: 0.13≤ R^2≤0.26 [with p-value significance]; large: R^2>0.26 [with p-value significance]) was examined.[5]
- DIF analyses were repeated using baseline and post-baseline data from US-based sites to assess the effect of culture/language on DIF direction.

Figure 1. Illustration of Uniform and Non-uniform DIF as Depicted in Zumbo 1999



Uniform DIF is in the same direction across the entire spectrum of the construct to be measured (e.g., asthma burden). Here at all levels of underlying construct, the likelihood of a specific response to an item is consistently higher for group 2 than for group 1. The ICCs are "parallel" to each other (i.e., non-crossing).[3]

Non-uniform DIF occurs when the difference between groups changes across different levels of the underlying construct. ICCs cross each other. The likelihood of item endorsement is higher for group 1 at lower levels of underlying construct, but the reverse is observed for higher levels.[3]

Objective

- To investigate if respondents with comparable health had a different probability of endorsing a response on the ACQ-5 and AQLQ due to their race and ethnicity.

Results

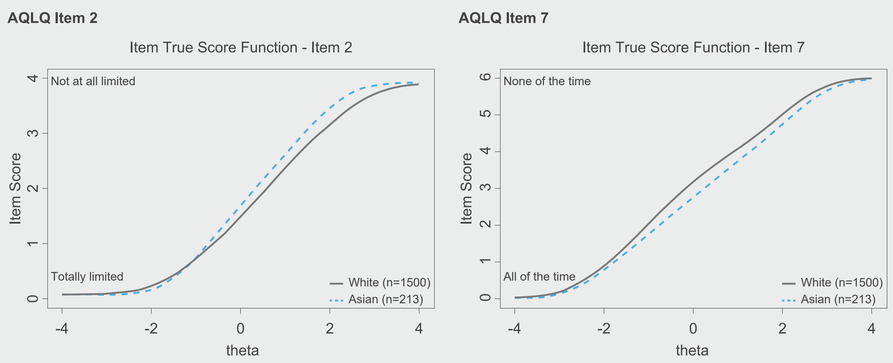
Global Analysis (All countries)

- 1902 participants were enrolled including:
  - 1412 non-Hispanic and 490 Hispanic;
  - 1577 White, 223 Asian, 80 Black/African American, and 22 other races.

Item level: ICC results

- ACQ-5 showed negligible underestimation of asthma symptom severity for non-Hispanic versus Hispanic, while there was negligible underestimation of asthma burden on quality of life for Hispanic for AQLQ (DIF for ACQ-5 and AQLQ were in opposite directions).
- No evidence of DIF between Black/African American and White for ACQ-5, while negligible DIF in opposite directions was observed for AQLQ.
- Negligible DIF in opposite directions between Asian and White for both ACQ-5 and AQLQ (see example of AQLQ items 2 and 7 in **Figure 2**).

Figure 2. Select ICCs for ACQ-5 and AQLQ across race groups (Asian and White) at baseline



Item 2 (range: 0-6, the higher the better): Limitation for Moderate activities?
Figure shows a negligible uniform DIF leading to an underestimation of asthma burden for Asian versus White.

Item 7 (range: 0-6, the higher the better): Do you feel concerned about your asthma?
Figure shows a negligible uniform DIF leading to an underestimation of asthma burden for White versus Asian.

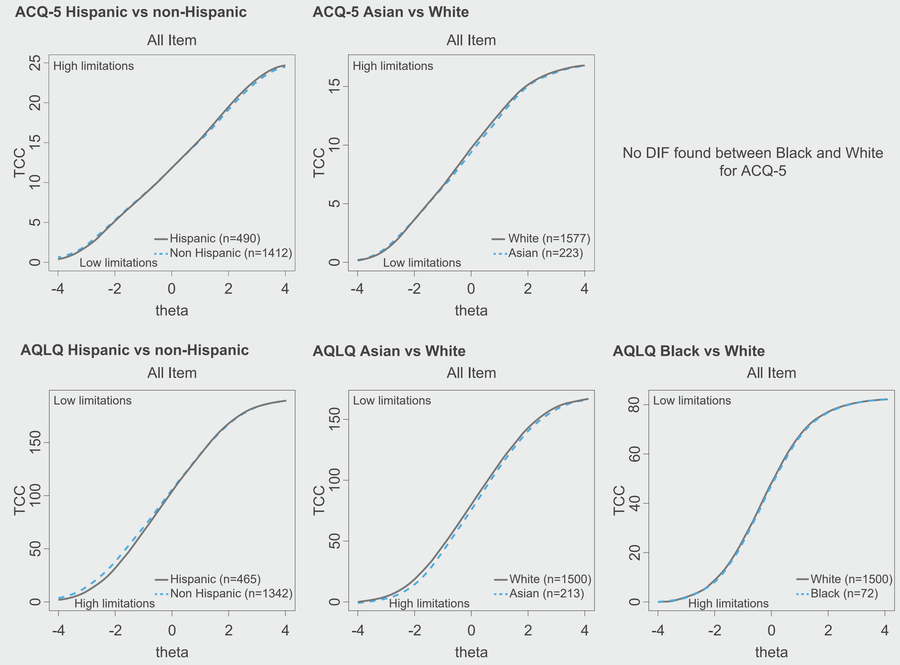
Scale level: TCC results

- TCCs for the global analysis illustrate the overall impact of negligible DIF on the ACQ-5 and AQLQ across the ethnic and racial groups (**Figure 3**).
- The overlapping of ethnic and racial groups curves suggests that similar responses in ACQ-5 or AQLQ scores were given for patients with similar asthma burden. The presence of negligible DIF did not impact the scores.

Analyses on patients enrolled in US sites (N=423)

- No evidence of DIF observed between Hispanic and non-Hispanic for ACQ-5, while negligible DIF were observed for AQLQ.
- No evidence of DIF observed between Black/African American and White for ACQ-5, while negligible DIF were observed for AQLQ.
- There was no evidence of DIF observed between Asian and White for ACQ-5, while negligible DIF in opposite direction were observed for AQLQ.

Figure 3. TCCs for ACQ-5 and AQLQ across racial and ethnic groups at baseline



Conclusions

- Important to evaluate if respondents have a different probability of endorsing a response on PRO measures due to their race and ethnicity to ensure that observed treatment benefits can be generalizable.
- Negligible DIF observed by racial and ethnic groups for both ACQ-5 and AQLQ, and DIF directions showed no consistent trends in the overall and US populations.
- These results support the use of ACQ-5 and AQLQ for assessing treatment outcomes in asthma clinical trials enrolling diverse racial and ethnic populations.

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