

Psychometric Validation of the QLQ-AA/PNH-54 Based on a Pooled Dataset of a Clinical Trial and Two Real-World Studies of Crovalimab in Participants with Paroxysmal Nocturnal Hemoglobinuria

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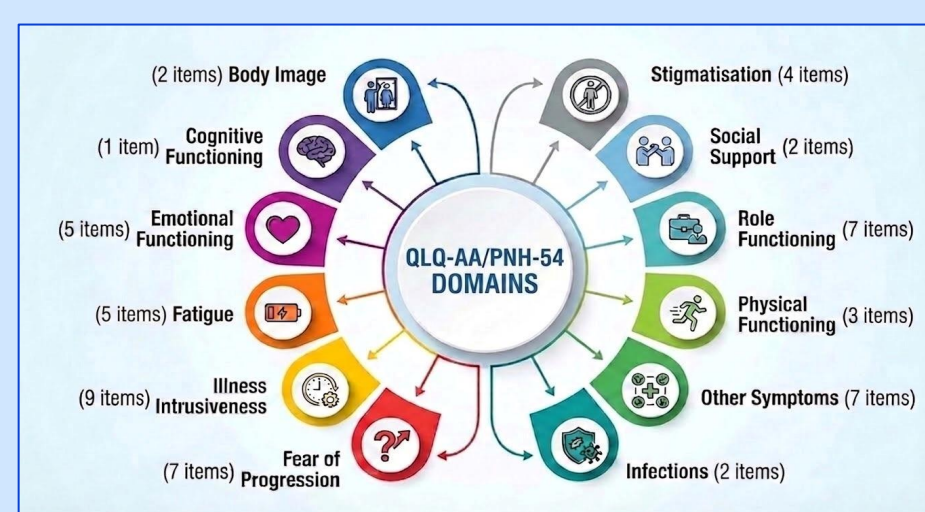
Summary

PNH is a rare, life-threatening, hematologic disorder. **Crovalimab**, a novel anti-C5 monoclonal antibody, was approved in 2024 for the treatment of PNH



~3,000-6,000 people are living with PNH in the USA [1]

The **QLQ-AA/PNH-54** was developed to assess HRQoL and symptoms in patients with PNH and AA



We used a pooled dataset to assess its psychometric properties

Summary of Results

Rating	Psychometric property	Comments
Green	Item-level characteristics	Excellent response distribution for all domains, only 4 items exhibited potential floor or ceiling effects, the majority of domains had good inter-item correlations
Green	Internal consistency	Excellent for the majority of domains, low for the 2 domains with few items
Yellow	Construct validity	Many strong correlations between domains as would be predicted, however some correlations were weaker than expected
Yellow	Effect sizes	Most domains had low-moderate effect sizes, however the analysis was limited due to few post-baseline assessments
Green	Meaningful change	Good results from the distribution-based method. Future research should examine an anchor-based approach to confirm findings
Red	Known groups validity, Test-retest reliability, Ability to detect change	These analyses couldn't be conducted because of limitations with the dataset (limited post-baseline data, lack of a proper categorization to establish known groups)

Rating: **Strong psychometric properties for all/most domains**, **Mixed results**, **Analysis not conducted**

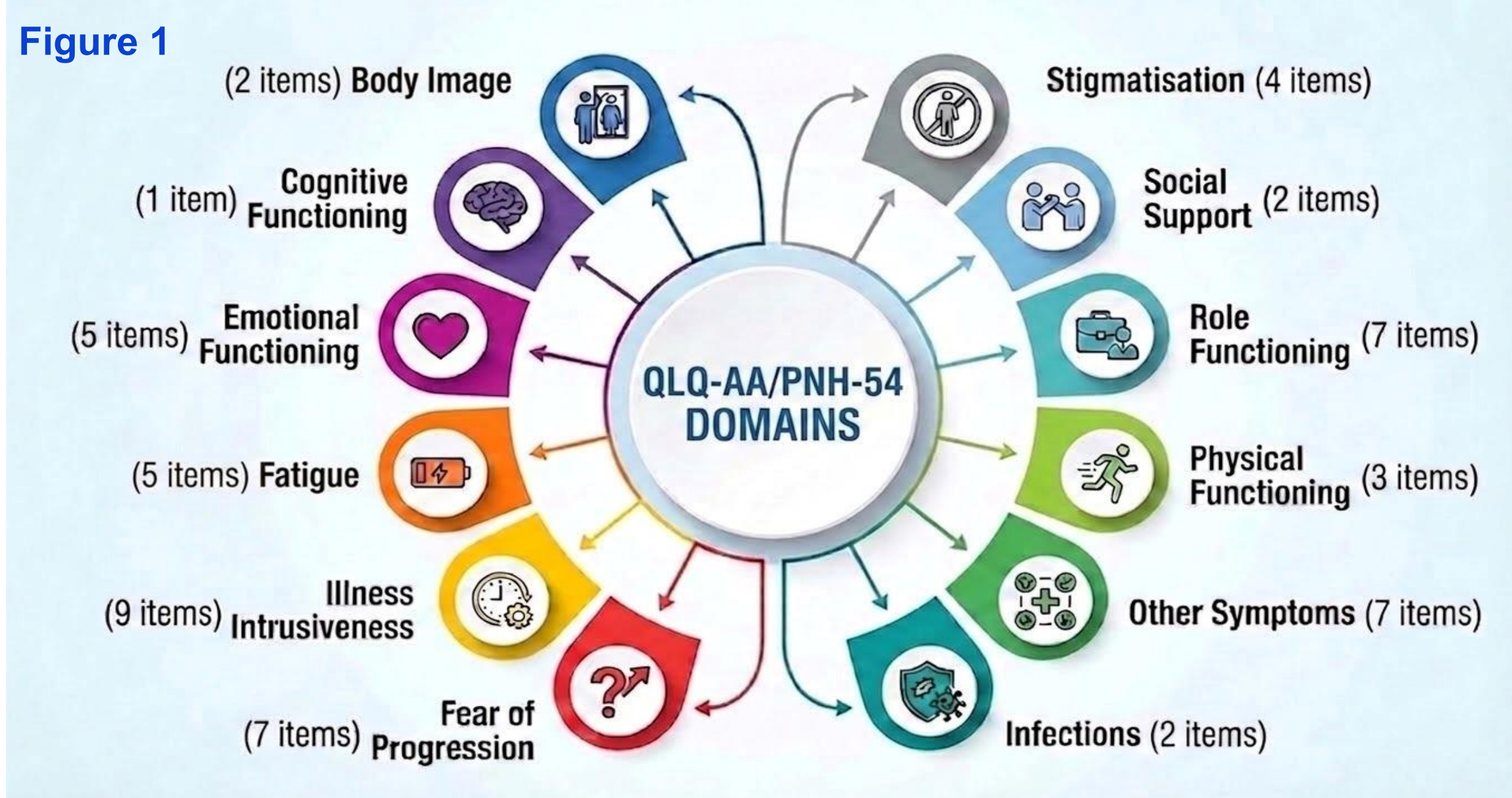
Background

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, life-threatening, hematologic disorder characterized by hemolysis, leading to anemia, fatigue, and other symptoms with an adverse impact on health-related quality of life (HRQoL) [1]
- Crovalimab (Piasky), a novel anti-C5 monoclonal antibody, was approved in 2024 for adult and pediatric patients (12- or 13- years and older, EMA and FDA, respectively) with PNH
- The QLQ-AA/PNH-54 is a patient-reported outcome (PRO) instrument developed to assess HRQoL in patients with PNH and acquired aplastic anemia (AA), two distinct but inter-related, ultra-rare hematological disorders.
 - Developed following the rigorous 4-phase process of the European Organisation for the Research and Treatment of Cancer (EORTC) group;
 - Content validation (phase III) was completed in 2019 [2]
- The crovalimab program included the QLQ-AA/PNH in 3 studies of PNH:
 - Phase 3 trial COMMODORE-2 (NCT04434092) (C-2)
 - COMMODORE-Burden of Illness (BOI) real-world (RW) study (C-BOI)
 - Picnic Health retrospective RW study of PNH (Picnic-PNH)

Here, the results of the initial phase IV psychometric analyses of the QLQ-AA/PNH-54 are presented

Methods

- The QLQ-AA/PNH-54 is composed of 54 items in 12 proposed domains (Figure 1)
 - Items are scored from 1 ("not at all") to 4 ("very much")
- The QLQ-AA/PNH-54 and EORTC QLQ-C30 were included in all 3 studies; the FACIT Fatigue was included in COMMODORE-2 and –BOI
- Psychometric analyses were conducted using the pooled dataset:
 - N=222 adult patients with PNH, 114 (51.4%) female
 - Mean age 41.9 years (range 18-88 years)
- Item-level descriptive characteristics were assessed: response distributions, floor & ceiling effects, and inter-item correlations
- Internal consistency and construct validity were assessed with Cronbach's alpha and Spearman correlations, respectively
- Standard deviations (SD) were calculated to provide a distribution-based estimate of meaningful change thresholds



Results: Item-level characteristics

- The minimum and maximum scores for 11 of the 12 domains covered the entire 0-100 range, indicating excellent response distributions
 - Other Symptoms domain exhibited a broad range from 0-90.5
- Means for each domain ranged from 33.3 (Social Support) to 52.6 (Fear of Progression); medians exhibited a similar range: 33.3 (Cognitive Functioning, Infections, Social Support) to 52.4 (Fear of Progression)
- Floor and ceiling effects were defined as >35% responses in the "not at all" or "very much" response options, respectively
 - 92.6% (50/54) items did not exhibit floor or ceiling effects
 - Floor effects were observed for 3 items: "increased tendency to bleed" and "problems with swelling and inflamed joints" (Other Symptoms domain), and "susceptible to infections" (Infections domain) while 1 item exhibited ceiling effects ("feel supported by family and friends, Social Support domain)

References

- Rare Disease Advisor, accessed April 10, 2026: <https://www.rarediseaseadvisor.com/disease-info-pages/paroxysmal-nocturnal-hemoglobinuria-epidemiology/#:~:text=Incidence%20and%20Prevalence%20of%20PNH,7%2C8>
- Niedeggen et al. Ann Hematol. 2019;98:1547-1559

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Results: Inter-item correlations

- Inter-item correlations demonstrate the strength of the relationships between the items that make up a domain. For 8 of the 11 domains (Emotional Functioning, Fatigue, Illness Intrusiveness, Infections, Fear of Progression, Physical Functioning, Role Functioning, and Stigmatization), moderate-to-strong inter-item correlations were observed for the majority of items. The Fatigue domain is shown as an example in Table 1:
 - The Other Symptoms domain had mostly low inter-item correlations
 - The Cognitive Functioning domain is 1 item and therefore not included

Table 1. Inter-item correlations for the Fatigue domain of the QLQ-AA/PNH-54

Fatigue domain items	Tired	Need to rest	Exhausted after exertion	Difficulty getting out of bed	No energy, sluggish
Were you tired	1	0.74	0.54	0.46	0.60
Need to rest	0.74	1	0.62	0.50	0.58
Exhausted after exertion	0.54	0.62	1	0.55	0.59
Difficulty getting out of bed	0.45	0.50	0.55	1	0.54
No energy, felt sluggish	0.60	0.58	0.59	0.54	1

The following benchmarks for interpreting the strength of the correlations were used: Negligible ≤ 0.29, Low 0.3 – 0.49, Moderate 0.5-0.69, High ≥ 0.70

- The items within the Social Support domain showed negligible inter-item correlations; this was also observed with the Body Image domain

Results: Construct validity

- Construct validity assesses the ability of a domain to measure the construct it was designed to evaluate. It is impacted by the number of items within the domain as well as the internal consistency of the domain
- The Cognitive, Emotional, Physical, and Role Functioning domains for the QLQ-AA/PNH-54 correlated most highly with their respective counterparts on the QLQ-C30
- However, the Social Support domain of the QLQ-AA/PNH-54 didn't correlate with the Social Functioning domain of the QLQ-C30, and the QLQ-AA/PNH-54 Fatigue domain correlated weakly with the FACIT Fatigue.

Table 2. Construct validity results

QLQ-AA/PNH-54 Domain	Facit Fatigue	GHS/QoL	Physical	Role	Emotional	Cognitive	Social
Body Image	-0.21	-0.39	-0.40	-0.41	-0.43	-0.39	-0.41
Cognitive Functioning	-0.25	-0.39	-0.60	-0.50	-0.60	-0.62	-0.47
Emotional Functioning	-0.38	-0.50	-0.65	-0.64	-0.78	-0.64	-0.63
Fatigue	-0.30	-0.60	-0.63	-0.62	-0.68	-0.56	-0.59
Illness Intrusiveness	-0.27	-0.57	-0.65	-0.66	-0.68	-0.62	-0.70
Infections	-0.29	-0.42	-0.49	-0.51	-0.59	-0.57	-0.61
Other Symptoms	-0.30	-0.44	-0.66	-0.60	-0.67	-0.65	-0.59
Fear of Progression	-0.28	-0.46	-0.48	-0.52	-0.58	-0.50	-0.59
Physical Functioning	-0.22	-0.53	-0.71	-0.65	-0.61	-0.57	-0.70
Role Functioning	-0.19	-0.55	-0.56	-0.66	-0.61	-0.50	-0.58
Social Support	-0.04	-0.25	-0.26	-0.30	-0.32	-0.28	-0.08
Stigmatization	-0.27	-0.53	-0.54	-0.64	-0.63	-0.59	-0.66

The following benchmarks for interpreting the strength of the correlations were used: Negligible ≤ 0.29, Low 0.3 – 0.49, Moderate 0.5-0.69, High ≥ 0.70

Results: Distribution-based meaningful change

- Meaningful change assesses the smallest degree of change that is noticeable to patients. Often, 0.5(SD) is used as an estimate for distribution-based methods.
- This ranged from 11.3 (Other Symptoms, Fear of Progression) to 15.5 (Cognitive Functioning)

Results: Internal consistency

- Internal consistency assesses the degree to which items in a test or scale are related to each other and measure the same construct. It is affected by the number of items in a domain
- Excellent internal consistency was observed for 8 domains (Table 3)

Table 3. Internal consistency results

Domain	Number of items	Cronbach's alpha	Lower 95% CI	Upper 95% CI
Body Image	2	0.35	0.16	0.50
Cognitive Functioning*	1	---	---	---
Emotional Functioning	5	0.88	0.85	0.90
Fatigue	5	0.87	0.84	0.89
Illness Intrusiveness	9	0.90	0.88	0.92
Infections	2	0.66	0.56	0.74
Other Symptoms	7	0.84	0.80	0.87
Fear of Progression	7	0.90	0.88	0.92
Physical Functioning	3	0.86	0.82	0.89
Role Functioning	7	0.81	0.76	0.84
Social Support	2	0.07	-0.21	0.29
Stigmatization	4	0.88	0.85	0.90

*The Cognitive Functioning domain is 1 item and therefore not assessed. The following were used to interpret Cronbach's alpha: Low 0.0 – 0.49, Moderate 0.5-0.69, Good 0.7-0.79, Excellent ≥ 0.80

Results: Effect sizes

- The effect size represents the size of the difference between the means of two groups. It is independent of sample size
- Small to medium effect sizes were observed for 9 of the domains

Table 4. Effect size results

Domain	n*	Baseline mean	Follow-up Mean	SD Baseline	Effect Size
Body Image	14	45.2	40.5	31.6	-0.15
Cognitive Functioning	15	33.3	24.4	39.8	-0.22
Emotional Functioning	14	39.0	24.3	34.2	-0.43
Fatigue	15	42.7	27.6	30.4	-0.50
Illness Intrusiveness	15	41.8	28.9	25.5	-0.51
Infections	15	38.9	35.6	40.7	-0.08
Other Symptoms	15	31.9	25.1	25.0	-0.27
Fear of Progression	15	44.4	33.3	30.9	-0.36
Physical Functioning	15	50.4	33.3	32.2	-0.53
Role Functioning	15	38.3	39.0	21.8	0.03
Social Support	14	22.6	31.0	24.1	0.35
Stigmatization	15	30.6	23.3	29.8	-0.24

*There were few post-baseline timepoints, and different times were used in the different studies. Existing post-baseline data was primarily from the C-2 study, at week 31 or 33. The following benchmarks for interpreting Cohen's d were used: Negligible ≤ 0.19, Small 0.2 – 0.49, Medium 0.5-0.79, Large ≥ 0.80

Conclusions

- We used a pooled dataset of 3 crovalimab studies of patients with PNH to evaluate the psychometric properties of the QLQ-AA/PNH-54
- Overall, the QLQ-AA/PNH-54 demonstrated strong psychometric properties for the majority of domains across multiple analyses
 - Weaker performance was observed for a few domains, most notably Social Support and Body Image, both of which are composed of only 2 items
- Limitations with the available dataset precluded certain analyses (e.g. test-retest reliability, known-groups validity). Limited post-baseline data was available, hampering the evaluation of ability to detect change. Additional research is needed to study these properties
- Based on these initial phase IV psychometric findings, the QLQ-AA/PNH-54 is appropriate for use to study the symptoms & HRQoL of patients with AA and PNH, and is recommended for use over non-disease-specific PROs

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