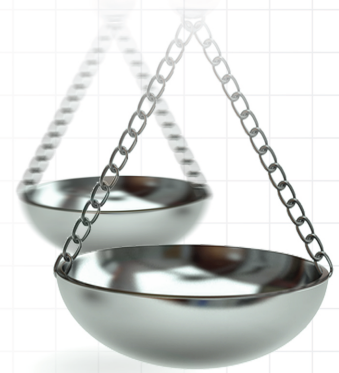




Mapping the EORTC QLQ-C30 onto the EQ-5D-5L index for patients with paroxysmal nocturnal hemoglobinuria in France

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Aim: To map patient-level data collected on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) QLQ-C30 to EQ-5D-5L data for estimating health-state utilities in patients with paroxysmal nocturnal hemoglobinuria (PNH). **Materials & methods:** European cross-sectional PNH patient survey data populated regression models mapping EORTC QLQ-C30 domains (covariates: sex and baseline age) to utilities calculated with the EQ-5D-5L French value set. A genetic algorithm allowed selection of the best-fitting between a set of models with and without interaction terms. We validated the selected algorithm using EQ-5D-5L utilities converted from EORTC QLQ-C30 data collected in the PEGASUS phase III, randomized controlled trial of pegcetacoplan versus eculizumab in adults with PNH. **Results:** Selected through the genetic algorithm, the ordinary least squares model without interactions provided highly stable results across study visits (mean [$\pm$ SD] utilities 0.58 [$\pm$ 0.42] to 0.89 [$\pm$ 0.10]), and showed the best predictive validity. **Conclusion:** The new PNH EQ-5D-5L direct mapping developed using a genetic algorithm enabled calculation of reliable health-state utility data required for cost-utility analysis in health technology assessments supporting treatments of PNH.

First draft submitted: 7 October 2022; Accepted for publication: 20 January 2023; Published online: 13 April 2023

Keywords: EORTC QLQ-C30 • EQ-5D-5L • paroxysmal nocturnal hemoglobinuria • utility mapping

Paroxysmal nocturnal hemoglobinuria (PNH) is an ultra-rare, acquired life-threatening hemolytic disorder with a global prevalence of approximately 1–1.5 cases per million [2–4]. Most frequently diagnosed in people aged 30–42 years [5,6]. When untreated, PNH is associated with a 10-year mortality rate of 24–29% [7,8]. Arising from genetic mutations of hemopoietic stem cells, PNH is characterized by intravascular hemolysis (IVH), extravascular hemolysis, bone marrow failure (e.g., aplastic anemia) and thrombocytosis [9,10]. Patients typically experience disabling fatigue, weakness, skin pallor, dyspnoea and increased heart rate [11–13]; these symptoms often warrant packed red blood cell (PRBC) transfusions to maintain patient daily life [12,14]. Because of its high disease activity [15], complications such as smooth muscle dystonia (presenting as abdominal pain, dysphagia, erectile dysfunction, etc.) [2,16] and impaired renal function [17,18] further add to the health related quality of life (HRQoL) and work productivity burden to patients and cost burden to healthcare systems [6,12,19,20].

Pegcetacoplan is a novel proximal C3 inhibitor (C3i) treatment for PNH [21], that has been recently approved for adults with PNH by the US FDA [22], and by the EMA [23] for adults with PNH who are anemic after treatment with a C5 inhibitor for at least 3 months [21]. PEGASUS (NCT 04085601) was the pivotal, phase III, prospective, multi-center, open-label, active-comparator, randomized controlled trial (RCT) of pegcetacoplan versus eculizumab, a first-generation complement monoclonal antibody C5 inhibitor (C5i) [24,25]. Whereas C5i

target the C5 component of the complement cascade to control IVH [26], C3i prevents C3b loading of red blood cells and subsequent extravascular hemolysis, in addition to controlling IVH [21].

Given constrained healthcare budgets, ensuring access to new drugs with high clinical effectiveness, is a global challenge for healthcare policy-makers [27]. From the payers perspective, any additional costs associated with introducing new medical technologies, even for indications with ultra-rare disease prevalence, must be justified by the associated clinical benefits. To address this concern, decision makers in many European healthcare jurisdictions rely upon evidence of the value of the new treatment in relation to the standard of care based on cost–utility analysis (CUA) [1,28–30]. CUA measures clinical benefit in terms of quality-adjusted life years (QALYs), as translated and standardized by patient health-state preferences or utility values. The QALYs can then be used to estimate the incremental cost–effectiveness ratio that is required to inform healthcare payers’ reimbursement decisions [1]. Collected using preference-based generic or disease specific instruments, utility values are derived from patient reported outcome data collected in trials or other types of studies. Generic instruments like the EQ-5D are preferred by HTA agencies because the data allow comparison across disease areas [1,29,30].

In PEGASUS, three instruments were administered to collect HRQoL data [31], including the disease specific 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [32] and The Functional Assessment of Chronic Illness Therapy (FACIT) fatigue [33] questionnaire, the most widely used HRQoL instruments used in cancer research [45] and also considered to demonstrate adequate reliability and validity in assessing PNH fatigue and HRQoL [32]. PEGASUS also included the Linear Analog Scale Assessment on which patients rate their perceived level of functioning, activity level and HRQoL [34]. However, the trial did not collect EQ-5D data necessary to facilitate a CUA for pegcetacoplan for the treatment of PNH to include in HTA submissions; therefore transforming the disease-specific HRQoL into EQ-5D-5L data was needed. Although it is possible to conduct mapping using existing mapping algorithms transforming EORTC QLQ-C30 to EQ-5D utilities, these are only available for a variety of oncological malignancies rather than for patients with PNH [35–38], especially given the ultra-rare prevalence and heterogeneous characteristics of the disease.

Therefore, this study aimed to develop a mapping algorithm estimating patient-level EQ-5D-5L utilities from EORTC QLQ-C30 data in patients with PNH. We followed good practice guidelines recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [39] and the Mapping onto Preference-based measures reporting Standards (MAPS) checklist for complete and transparent reporting of mapping studies [40,41].

Materials & methods

Targeted literature search

To ensure the need for a utility mapping algorithm specifically for use in the PNH population, we conducted a targeted search and found that there was no relevant algorithm published.

Estimation sample

To enable the mapping, we obtained data from an external online cross-sectional, ethics approved European PNH patient survey conducted in France, Germany and the UK between 1 January and 31 March 2021 [42]. The survey identified participants from physician referrals, social media and patient advocacy groups. A convenience sample of 90 adult patients (30 from each country) was sought, comprising those with a self-reported diagnosis of PNH, currently treated with eculizumab or ravulizumab, who agreed to provide informed consent and adverse event reporting were invited to take part in the 25 min one-time survey. The survey paid patients a fair value fee for their time and participation.

In addition to providing information on their HRQoL, as reported on the EORTC QLQ-C30 and EQ-5D-5L, patients also provided data on their demographic and baseline clinical characteristics, including the most recent serum Hb level and history of PRBC transfusions. The anonymized patient data were stored on a secure server and then transmitted directly to statistical software (R version 4.0.5), using stats, ALDMM, GAMLSS and GAMLSS dist for analyses.

Validation sample

For validating the algorithm, we used the patient data from the PEGASUS trial of pegcetacoplan. In PEGASUS, following 1:1 randomization, patients received either pegcetacoplan ($n = 41$) at a dose of 1080 mg sc. (twice weekly or every 3 days) or eculizumab ($n = 39$) administered by intravenous infusion at the current and stable prescribed

dosage. After a 4 week run-in period, the trial continued with a 16-week randomized controlled period (RCP) [21]. Using the selected mapping algorithm, we calculated utilities for each patient at each clinical visit in PEGASUS. Visits included at baseline, every 2 weeks until week 8, and thereafter at weeks 12 and 16 during the RCP, followed by a 32-week open-label period comprising a second run-in period and in which patients administered eculizumab also received concomitant pegcetacoplan for 4 weeks and only pegcetacoplan thereafter.

Following the mapping exercise, EQ-5D-5L health-state utilities were calculated using patient-level EORTC QLQ-C30 data; these values inform the analytic model examining the cost-utility of pegcetacoplan versus eculizumab or ravulizumab in adults with PNH and Hb levels <10.5 g/dl despite receiving stable doses of eculizumab for at least 3 months [21]. The CUA model, based on a Markov cohort framework (Supplementary Figure 1), spanned a lifetime (51 years) horizon comprising 4-week cycle lengths. Within the model, patients could transition between four mutually exclusive health states that represented patient disease status (in addition to death), in terms of Hb level and blood transfusion requirement:

- Transfusion-dependent (TD) if requiring transfusion within preceding 4 weeks (including the 4 week run-in period applied at model entry)
- Transfusion-avoidant (TA) if not requiring transfusion within preceding 4 weeks; or
- Subcategorized TA according to the level of Hb (≥ 10.5 g/dl; <10.5 g/dl).

As patient status could change during the RCT (e.g., a TA patient could become TD and *vice versa* during the 16-week period), patient health-state utilities were adapted accordingly, with the status of each patient and associated health state re-evaluated at the beginning of each 4-week cycle of the CUA model.

Source & target measures

The EORTC QLQ-C30, the source measure used for the mapping, assesses important domains of functioning (including physical [PF], cognitive [CF], emotional [EF], role [RF], social [SF]), common symptoms (including fatigue [FA], nausea and vomiting [NV], pain [PA], dyspnoea [DY], insomnia [SL], appetite loss [AP], constipation [CO] and diarrhea [DI]) and other outcomes such as financial difficulties (FI) and global quality of life (QL) related to cancer [43,44]. Scores for EORTC QLQ-C30 are summarized on five functioning subscales, nine symptom subscales scores and a global health status score.

The EQ-5D, the target measure, evaluates five dimensions of HRQoL, including mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Depending on the version of EQ-5D, the severity of each dimension can be assessed via a three-level (EQ-5D-3L or EQ-5D-Y-3L [youth version]) or five-level (EQ-5D-5L) [45] response scale. This allows the investigator to estimate health-state utilities by applying country specific value sets to the combination of responses collected by the questionnaire. A utility score of 1 represents perfect health and 0 corresponds to health states that are comparable to death; negative values are also possible and represent health states worse than death, as based on patients preferences.

Missing data

While built-in prompts avoided missing data, the final source dataset included all available data including individuals who stopped partway through the survey; no imputations were conducted for any missing data. The database was checked throughout the fielding process to ensure that the patients were answering the survey as intended.

Modeling approaches

Following a direct mapping approach [39], we converted EORTC QLQ-C30 responses to EQ-5D-5L index values using the EQ-5D-5L French value set and fitting various regression models [39].

We first tested three regression models, including an ordinary least squares (OLS) model, an adjusted limited dependent variable mixture (ALDVM) model and a beta-inflated distribution for fitting the generalised additive model for location scale and shape (GAMLSS) (Supplementary Table 1). Analyses were conducted using the ALDVM software package.

Three combinations of independent variables were then applied for each regression technique:

- A full model, including all EORTC domains and baseline age and sex as covariates, without interactions between variables:

EQ-5D-5L utility = age + sex + QL + PF + RF + EF + SF + CF + FA + NV + PA + DY + SL + AP + CO + DI + FI

- A restricted model, without interactions, including EORTC variables selected using a ‘genetic algorithm’, assuming no interactions between variables:
EQ-5D-5L utility = PF+EF+SF+PA (all regressions);
EQ-5D-5L utility = PF+EF+SF+FA+DI (only beta regressions)
- A restricted model with interactions, whereby we selected the variables and interactions using a ‘genetic algorithm’:
EQ-5D-5L utility = DI*DY+DY*FA+DY*RF+FA*FI+FI*SF+NV*PA+PA*PF+PA*SF+PA*SL+sex*SL (only for linear and ALDVM model regressions)

Genetic algorithms are a method of optimization involving iterative search procedures based on an analogy with evolutionary genetics [46]. The algorithm comprises three main phases:

- Generation of the initial pool of unique models with random structures encoded on ‘chromosomes’.
- Recombination: Two randomly selected individual models exchange the information encoded in their chromosomes through a crossover process, leading to generation of individual offspring models.
- Selection: All models are tested for fitting to the data (selection pressure) using a Schwartz (or Bayesian) information criterion (BIC). Preferred models have lower BIC, representing better trade-off between model fit and parsimony (i.e., minimal number of independent variables). In this stage, if the offspring model presents superior performance, it replaces the parent models in the pool. If not, the parent models return to the pool.

Measures of model performance

For each type of regression, we selected models with lower BIC; this criterion; however, was not suitable to compare between various regressions due to differences in likelihood functions. Therefore, we used a lower root-mean-square error (RMSE) as the criterion for model fit and compared the performance between different regressions. The best-fitting model was then used to estimate EQ-5D-5L utilities from EORTC QLQ-C30 data from PEGASUS; thereafter, utilities were calculated for health states and applied to the pegcetacoplan CUA conducted from the French healthcare system perspective.

Derivation of health state utilities

For the choice of model, we considered that utility values could not be greater than 1 (i.e., required censoring), hence, we estimated health state-associated utilities using a Tobit regression model, allowing for multiple measurements:

$$\text{Utility} = \text{Health state}_{\text{current}} + \text{Age} + \text{Visit} + u_i$$

The current health state (i.e., the health state at the respective visit), age and visit category were fixed-effects variables; a random effects intercept at patient level (u_i) was also specified. We categorized the assessments during PEGASUS as: 1 × screening (up to 12 weeks before randomized control period [RCP]); 2 × run-in period (4 weeks before RCT); 7 × RCT period (16 weeks); 7 × open-label period (32 weeks); 3 × follow-up period (7 weeks). This categorization was considered since descriptive analysis suggested that utilities vary between visits, and health states are expected to vary between visits. Therefore, we classified visit a potential confounder when evaluating the association between health state and utility.

We computed health-state utilities for the 10.5 g/dl Hb threshold by summing the intercept and parameter estimates for health state, visit and age multiplied by 48.8 years (mean age of survey respondents).

Validation methods

Results of the Tobit model were first validated through comparison with a linear mixed-effects model. We further validated the mapped utility values through comparison with the utility values calculated using the indirect mapping algorithm published by Longworth *et al.* (2014) [1], which maps EORTC QLQ-C30 scores to EQ-5D-3L scores.

Table 1. Patient characteristics.

Characteristics (n = 71)		
Age (years; mean, $\pm$ SD)	43.0	$\pm$ 13.1
Sex (female; n, %)	47	66.2%
Age at diagnosis (years; mean, $\pm$ SD)	29.8	$\pm$ 11.6
Time from diagnosis (years; mean, $\pm$ SD)	13.2	$\pm$ 8.8
Total serum hemoglobin (g/dl; mean, $\pm$ SD)	10.2	$\pm$ 2.0
Aplastic anemia/severe aplastic anemia (n, %)	26	36.6%
Myelodysplastic syndrome (n, %)	1	1.4%
Other bone marrow disorder (n, %)	4	5.6%
SD: Standard deviation.		

Table 2. Distributions of EORTC QLQ-C30 subscale and EQ-5D-5L index scores.

Variable	Abbreviation	Mean	$\pm$ SD	Median	[min; max]	Interquartiles [Q1; Q3]
EORTC QLQ-C30						
Global health	QL	66.9	$\pm$ 20.2	66.7	[16.7; 100]	[50; 83.3]
Physical functioning	PF	83.2	$\pm$ 18.5	86.7	[20; 100]	[73.3; 100]
Role functioning	RF	70.0	$\pm$ 32.2	66.7	[0; 100]	[50.0; 100]
Emotional functioning	EF	75.2	$\pm$ 24.4	83.3	[8.3; 100]	[58.3; 100]
Cognitive functioning	CF	73.9	$\pm$ 26.1	83.3	[0; 100]	[66.7; 100]
Social functioning	SF	71.6	$\pm$ 30.7	66.7	[0; 100]	[50.0; 100]
Fatigue	FA	42.6	$\pm$ 28.3	33.3	[0; 100]	[22.2; 66.7]
Nausea and vomiting	NV	5.9	$\pm$ 12.6	0	[0; 66.7]	[0; 0]
Pain	PA	19.5	$\pm$ 23.6	16.7	[0; 100]	[0; 33.3]
Dyspnea	DY	29.6	$\pm$ 28.5	33.3	[0; 100]	[0; 66.7]
Insomnia	SL	30	$\pm$ 31.9	33.3	[0; 100]	[0; 33.3]
Appetite loss	AP	11.7	$\pm$ 22.6	0	[0; 100]	[0; 33.3]
Constipation	CO	8	$\pm$ 19.1	0	[0; 100]	[0; 0]
Diarrhea	DI	7	$\pm$ 21.8	0	[0; 100]	[0; 0]
Financial difficulties	FI	17.8	$\pm$ 29.2	0	[0; 100]	[0; 33.3]
EQ-5D-5L						
Utility scores (based on French value set)		0.73	$\pm$ 0.26	0.77	[-0.02; 1.00]	[0.56; 0.93]
VAS		69.9	$\pm$ 16.9	72	[30; 95]	[60; 81]
Domain levels:	Patients rating level 3 or above on item (%)			Median	[min; max]	Interquartiles [Q1; Q3]
Mobility	16.9%			1	[1; 4]	[1; 2]
Self-care	8.5%			1	[1; 3]	[1; 1]
Activity	28.2%			2	[1; 5]	[1; 3]
Pain	28.2%			2	[1; 4]	[1; 3]
Anxiety	21.1%			2	[1; 5]	[1; 2]

AP: Appetite loss; CF: Cognitive functioning; CO: Constipation; DI: Diarrhea; DY: Dyspnea; EF: Emotional functioning; FA: Fatigue; FI: Financial difficulties; NV: Nausea and vomiting; PA: Pain; PF: Physical functioning; QL: Quality of life; RF: Role functioning; SD: Standard deviation; SF: Social functioning; SL: Insomnia; VAS: Visual analogue scale.

Results

Estimation sample

In total 71 patients from France (n = 20 [28.2%]), Germany (n = 31 [43.6%]) and the UK (n = 20 [28.2%]) completed the PNH cross-sectional survey. Women comprised 66.2% of the survey sample and the mean age (standard deviation) of the full sample was 43.0 ($\pm$ 13.1) years. The mean age at PNH diagnosis was 29.8 ($\pm$ 11.6) years. The mean serum Hb level was 10.2 g/dl ($\pm$ 2.0), and aplastic anemia, which was identified in 36 patients, was the most common PNH related comorbidity (36.6%). Self-reported Hb levels, recorded by 63 patients (88.7%) in the survey, showed that 57.1% (n = 36) had Hb <10.5 g/dl, whereas the remaining 42.9% (n = 27) had Hb $\geq$ 10.5 g/dl (Table 1). On the EQ-5D-5L, 28.2% of patients scored a level of 3 or above (Table 2) for the domains Pain and Activity, respectively and 21.1% for anxiety, 16.9% for mobility and 8.5% for self-care. The

mean EQ-5D-5L index score was 0.73 (± 0.26) and the median was 0.77 (range: -0.02; 1.00) (Supplementary Figures 2 & 3).

Model selection

As selected through a genetic algorithm, the OLS regression model with the combination of variables and interactions showed the best performance, yielding the lowest BIC (-119.3433) and RMSE (0.0523) values (Table 3 & Supplementary Figure 4). All OLS models were accurate in predicting utilities from the survey sample, with mean utility (0.73), standard deviations (0.25–0.26), medians (0.79–0.82) and interquartiles (0.59–0.92) all within reasonable ranges (Table 4). However, the beta inflated models slightly underestimated the mean (0.68) and median (0.74) utility values, with a narrow interquartile range of predicted values (0.58; 0.82) compared with the survey data.

Applied to PEGASUS trial data, the range of results (-1.71–1.25) based on the OLS model with interactions produced large standard deviations and an invalid (i.e., values > 1) upper range of utilities compared with utility values estimated with the OLS model without interactions (range: -0.16–0.98) (Table 4); hence, we rejected the OLS model with interactions and did not apply it for further utility mapping. Instead, we deemed the OLS model without interactions as the best fitting and most suitable for further analysis.

Using the best-fitting model, (i.e., the OLS without interactions), mean ($\pm$ SD) utilities mapped using the EQ-5D-5L French value set ranged between 0.58 (± 0.42) and 0.89 (± 0.10) (medians [q1; q3] ranged between 0.58 [0.44; 0.73] and 0.91 [0.88; 0.95]) across the PEGASUS study visits, with individual values ranging from -0.16–0.98 (Table 5 & Supplementary Figure 5). Based on the Tobit model, the estimate for the reference patient when all covariates are null was 0.807 ($p < 0.001$); parameter estimates for health states TA (Hb <10.5 g/dl) (0.045; $p = 0.0003$) and TA (Hb ≥ 10.5 g/dl) (0.141; $p < 0.0001$) were significantly higher compared with the reference state (TD), with significantly lower utility estimates for all study periods compared with visit 1. For the age parameter, there was a trend toward decreasing utility in older patients. In estimating utilities for each PNH health state, both the Tobit regression model and the linear mixed-effect models were comparable in terms of estimated health-state utilities (Supplementary Table 2).

Utility estimates for the model health states TD; TA (Hb <10.5 g/dl); and TA (Hb ≥ 10.5 g/dl) derived from the Tobit model were 0.644, 0.689 and 0.784, respectively; and comparable to the linear mixed-effects model: 0.644, 0.688 and 0.784, respectively (Supplementary Table 3). Hence, both models produced the same results and the choice of Tobit model had virtually no impact on the analysis. Against the PNH EQ-5D-3L health-state utilities estimated using the Longworth *et al.* (2014) algorithm (Table 6), the utility values estimated on the linear mixed-effects model provided comparable results. The Longworth algorithm provided mean PNH health-state utility estimates (standard errors) of 0.673 (0.022) for TD; 0.722 (0.021) for TA, Hb <10.5 g/dl; and 0.809 (0.021) for TA, Hb ≥ 10.5 g/dl. The mixed-effects model provided estimates of 0.644 (0.024) for TD; 0.689 (0.023) for TA, Hb <10.5 g/dl; and 0.784 (0.023) for TA, Hb ≥ 10.5 g/dl.

Discussion/conclusion

In this study, we conducted utility mapping using genetic algorithms which are powerful analytic tools that can be used to rapidly select best-fitting regression models. Notwithstanding the challenges of conducting utility mapping based on studies with a limited number of subjects, as is inherent in rare diseases such as PNH, the genetic algorithm enabled us to address a utility data gap and rigorously estimate EQ-5D-5L utility data for application to economic evaluations in PNH. We followed ISPOR good practice guidelines for mapping to estimate health-state utility from non preference-based outcome measures [39], including validation of the algorithm with a sample separate from the estimation sample [47]. We report our research based on the MAPS checklist for complete and transparent reporting of mapping studies [40,41].

The genetic algorithm employed tested three regression models using EQ-5D-5L French utilities as the dependent variable and EORTC QLQ-C30 domains as independent variables and sex and baseline age as covariates, separately specified with and without interaction terms. The OLS model with interactions provided the best fit; however it produced a significant number of utility estimates that were above 1 when fitted with the PEGASUS data. However, the predicted utilities using the model without interactions on the other hand produced utility estimates that did not exceed 1 [1,47,48]; therefore we examined this latter model in further analyses. Compared with EQ-5D-3L utilities estimated using the well-established Longworth *et al.* algorithm, the OLS mixed-effects model applied to the EORTC QLQ-C30 data from PEGASUS provided highly comparable results.

Table 3. Model performance.

Parameter	OLS	ALDVMM	Beta	
Model without interaction: ~PF+EF+SF+PA				
BIC	-109.1490	145.9671	-2.2471	
RMSE	0.0937	0.2170	0.1075	
		Component 1	Component 2	
Intercept	0.057019	-0.012	0.009	-2.166011 [§]
PF	0.0052616 [§]	0.003	-0.026	0.02636 [§]
EF	0.0018992 [‡]	0.018	0.028	0.005035
SF	0.0021061 [‡]	-0.007	0.065	0.011241 [†]
PA	-0.0031849 [§]	-0.011	0.152	-0.010323 [†]
Insignia	–	-0.607	0.118	-
Model with interactions: ~DI*DY+DY*FA+DY*RF+FA*FI+FI*SF+NV*PA+PA*PF+PA*SF+PA*SL+sex*SL				
BIC	-119.3433	409.6680	Model could not be calculated	
RMSE	0.0523	0.2228		
		Component 1	Component 2	
Intercept:	0.7324 [§]	0.05	0.025	
DI	-0.0003352	0	0	
DY	-0.01322 [§]	0	0	
FA	-0.003882 [§]	0	0	
RF	-0.002325 [†]	0.005	0.013	
FI	-0.009829 [§]	0	0	
SF	0.003036 [‡]	0.006	0	
NV	0.005138 [‡]	0	0	
PA	0.003004	0	0	
PF	0.00193	0	0	
SL	0.0001679	0	0	
Sex	0.04378	0	0	
DI:DY	0.00004093 [‡]	0	0	
DY:FA	0.00009337 [‡]	0	0	
DY:RF	0.000125 [§]	0	0	
FA:FI	0.00007257 [‡]	0	0	
FI:SF	0.00009712 [§]	0	0	
NV:PA	-0.0001801 [§]	0	0	
PA:PF	0.00005303	0	0	
SF:PA	-0.00009554 [‡]	0	0	
PA:SL	-0.00005086 [‡]	0	0	
SL:sex	-0.00216 [‡]	0	0	
Insignia	–	0	0	
Full model				
BIC	-65.4925	352.3485	Model could not be calculated	
RMSE	0.0862	0.1778		
		Component 1	Component 2	
Intercept	0.1382	-0.003	0.004	
age	0.0002534	0.001	-0.012	
sex	0.008817	0	0.005	
QL	0.000298	0.002	0.004	
PF	0.004333 [‡]	0.002	-0.004	

[†]p < 0.01.

[‡]p < 0.001.

[§]p < 0.0001.

ALDVM: Adjusted limited dependent variable mixture; BIC: Bayesian information criterion; DI: Diarrhea; DY: Dyspnea; EF: Emotional functioning; FA: Fatigue; FI: Financial difficulties; NV: Nausea and vomiting; OLS: Ordinary least squares; PA: Pain; PF: Physical functioning; RF: Role functioning; RMSE: Root-mean-square error; SF: Social functioning; SL: Insomnia.

Table 3. Model performance (cont.).

Full model			
RF	0.001421	0.003	0.001
EF	0.002243 [†]	0.002	0.001
SF	0.001306	0.003	0.002
CF	-0.00103	0.002	0.001
FA	-0.00006987	0	0
NV	0.0008919	-0.001	0.004
PA	-0.002279 [‡]	0	0.001
DY	-0.0009444	0	-0.001
SL	-0.0007174	-0.001	0.024
AP	-0.0009358	0	0.001
CO	0.0002667	0.001	0.003
DI	0.0005363	0.001	0.01
FI	0.0002863	0	0.001
Insigma	–	-0.058	0.003

[†]p < 0.01.[‡]p < 0.001.[§]p < 0.0001.

ALDVM: Adjusted limited dependent variable mixture; BIC: Bayesian information criterion; DI: Diarrhea; DY: Dyspnea; EF: Emotional functioning; FA: Fatigue; FI: Financial difficulties; NV: Nausea and vomiting; OLS: Ordinary least squares; PA: Pain; PF: Physical functioning; RF: Role functioning; RMSE: Root-mean-square error; SF: Social functioning; SL: Insomnia.

Table 4. Predicted EQ-5D-5L utilities.

Summary statistics of OLS models	Observed EQ-5D-5L values	Full model	Model without interactions	Model with interactions	Best from genetic algorithm
Survey data					Beta inflated
Mean (SD)	0.73 (0.26)	0.73 (0.25)	0.73 (0.25)	0.73 (0.26)	0.68 (0.18)
Median [q1; q3]	0.77 [0.56; 0.93]	0.82 [0.59; 0.92]	0.79 [0.59; 0.92]	0.81 [0.59; 0.91]	0.74 [0.58; 0.82]
Range	(-0.024; 1.00)	(0.05; 1.01)	(0.00; 0.98)	(-0.04; 1.04)	(0.17; 0.86)
BIC	–	-65.4925	-109.1490	-119.3433	-46.6086
RMSE	–	0.0862	0.0937	0.0523	0.1342
Mapped PEGASUS data					
Mean (SD)	(Missing)	0.76 (0.24)	0.74 (0.24)	0.74 (0.32)	0.69 (0.17)
Median [q1; q3]		0.82 [0.64; 0.95]	0.81 [0.63; 0.93]	0.84 [0.67; 0.94]	0.75 [0.62; 0.82]
Range		[-0.17; 1.07]	[-0.16; 0.98]	[-1.71; 1.25]	[0.10; 0.89]

BIC: Bayesian information criterion; OLS: Ordinary least squares; RMSE: Root-mean-square error; SD: Standard deviation.

The PEGASUS pivotal trial of pegcetacoplan, in which 80 adults with PNH were randomised 1:1 to the treatment arms, showed that pegcetacoplan was superior to eculizumab in terms of improvement of Hb levels from baseline, decrease in PRBC transfusions decrease in total reticulocyte counts and with comparable safety [21,49]. PEGASUS also showed clinically meaningful improvements in FACIT fatigue scores and HRQoL measured with the EORTC QLQ-C30 compared with eculizumab [21,49]. However, data were not available from the trial to translate the HRQoL benefits into utilities to measure the overall health economic benefits of pegcetacoplan. Hence, disease specific HRQoL instruments, such as the EORTC QLQ-30, although sensitive for assessing outcomes in cancer patients and also considered to demonstrate adequate reliability and validity in assessing PNH fatigue and HRQoL [32], do not provide generic utilities required for CEA to inform HTA. Such data are needed by payers to assess whether incremental cost–effectiveness ratio fall within a defined willingness-to-pay threshold that applies across conditions [50,51].

Where there is a generic preference-based data shortfall within the study that informs the clinical parameters of the CEA model, mapping methods allow researchers to overcome the problem of missing datasets by converting the disease specific HRQoL data into generic utilities [47]. Yet, for rare diseases such as PNH, where the HRQoL data have been collected on the EORTC QLQ-C30, there are no dedicated algorithms as there are for cancer patient

Table 5. Utilities calculated using best-fitting model at each clinical visit.

Visit	Utility calculated with a linear regression model without interactions			
	n	Mean [min; max]	±SD	Median [q1; q3]
Screening	2	0.67 [0.66; 0.67]	±0.01	0.67 [0.66; 0.67]
Week 4	76	0.65 [-0.03; 0.98]	±0.24	0.70 [0.52; 0.84]
Week 2	75	0.77 [0.15; 0.98]	±0.21	0.83 [0.65; 0.92]
Day 1	77	0.83 [0.32; 0.98]	±0.16	0.88 [0.76; 0.97]
Week 2	77	0.74 [-0.12; 0.98]	±0.24	0.81 [0.62; 0.91]
Week 4	76	0.68 [-0.07; 0.98]	±0.28	0.79 [0.51; 0.89]
Week 6	76	0.72 [-0.16; 0.98]	±0.25	0.78 [0.62; 0.88]
Week 8	75	0.73 [-0.14; 0.98]	±0.25	0.81 [0.63; 0.91]
Week 12	75	0.73 [-0.01; 0.98]	±0.25	0.81 [0.60; 0.91]
Week 16	74	0.70 [-0.03; 0.98]	±0.25	0.76 [0.61; 0.90]
Week 17	74	0.71 [-0.09; 0.98]	±0.26	0.78 [0.58; 0.91]
Week 18	74	0.75 [-0.02; 0.98]	±0.23	0.84 [0.65; 0.92]
Week 20	75	0.75 [-0.09; 0.98]	±0.24	0.82 [0.65; 0.93]
Week 22	74	0.79 [0.07; 0.98]	±0.20	0.85 [0.72; 0.93]
Week 24	72	0.77 [0.00; 0.98]	±0.24	0.85 [0.65; 0.95]
Week 28	73	0.74 [0.00; 0.98]	±0.25	0.80 [0.65; 0.94]
Week 32	72	0.77 [-0.16; 0.98]	±0.24	0.85 [0.65; 0.95]
Week 36	69	0.77 [0.10; 0.98]	±0.24	0.87 [0.67; 0.98]
Week 40	62	0.78 [0.03; 0.98]	±0.22	0.86 [0.63; 0.95]
Week 44	62	0.72 [0.02; 0.98]	±0.25	0.82 [0.58; 0.91]
Week 48	59	0.77 [-0.02; 0.98]	±0.22	0.86 [0.63; 0.93]
Week 54	7	0.89 [0.69; 0.98]	±0.10	0.91 [0.88; 0.95]
Week 60	2	0.58 [0.29; 0.88]	±0.42	0.58 [0.44; 0.73]

SD: Standard deviation.

Table 6. Utility values estimated by Longworth *et al.* (2013) algorithm and the estimated linear mixed-effects model.

Health state	Utility value	Standard error	Lower CI	Upper 95% CI	Ref.
Longworth (EQ-5D-3L utilities)					[47]
TD	0.673	0.022	0.630	0.716	
TA, Hb <10.5 g/dl	0.722	0.021	0.680	0.763	
TA, Hb ≥10.5 g/dl	0.809	0.021	0.768	0.851	
Linear mixed-effects model (EQ-5D-5L utilities)					
TD	0.644	0.024	0.597	0.691	
TA, Hb <10.5 g/dl	0.689	0.023	0.643	0.735	
TA, Hb ≥10.5 g/dl	0.784	0.023	0.739	0.830	

Hb: Hemoglobin; TA: Transfusion avoidant; TD: Transfusion dependent.

populations; moreover, the limited population of PNH patients pose further methodological issues for deriving *de novo* algorithms which we describe below.

Mapping HRQoL data to utilities is usually conducted with regression analyses to allow additional covariates such as patient socio-demographics and/or extrapolation beyond the range of disease severity observed in the source data, in particular for lifetime CEA models such as in PNH [39]. Two sets of approaches are available for mapping EQ-5D utilities using regression analysis. The direct approach converts EQ-5D-5L responses to EQ-5D-5L index values using a country-specific value set and various regression models are fitted. Alternatively, the indirect, two-stage method first maps patient EORTC QLQ-30 scores on their response to the EQ-5D-5L domains via a regression equation. In the second stage, country specific value sets allow estimating country specific utility values. Since the regression equation is universal, the first stage of mapping does not need to be repeated when estimating scores for different countries. Compared with the direct method, the limitation of indirect response mapping is that it requires

more sophisticated calculations, using a series of separate regression models to estimate responses for each domain of EQ-5D scores, which thus requires larger samples to allow for the precise estimation of utility scores [52]. Hence, direct mapping algorithms are useful in these instances of limited estimation sample sizes [52]. By also testing an OLS model with ALDVM model and a beta-inflated distribution for fitting the GAMLSS, we have also considered the inherent distributional features of utilities in PNH [39,53,54].

Data collected within a PNH patient survey facilitated our direct mapping study, having both the disease-specific HRQoL data from the EORTC QLQ-30 and the single index values (utilities) from the EQ-5D-5L collected from respondents. Deriving utilities from the real-world study provided other benefits. Although data collected from RCTs can provide data with a high level of internal validity with which to examine relationships between an intervention and measured outcomes [55], the trial population may not represent individuals in real-world clinical practice. Exclusion criteria for such aspects as comorbidities and disease severity outside of the trial inclusion criteria create a highly homogenous study population. This contrasts with the needs of payers who prefer to assess healthcare interventions on broad and real-world patient populations and their economic performance in a naturalistic setting [56]. Therefore, by deriving utilities for a real-world sample of patients with PNH and applying French societal values, this study has provided more generalisable utility values than derived from RCTs to apply to the pegcetacoplan CUA estimates from the French healthcare perspective [39].

For our analysis, we considered that multi component ALDVMMs models may provide best fit. However, due to very small sample and high computational requirements we tested 2-component ALDVMM models [52]. The mixture models we specified for the mapping also took into account the non-standard distributional characteristics of EQ-5D which have been observed to have a tendency to result in bias, whereby QALYs are reduced and the technology appears less cost-effective than its true value [57]. Hence, the use of mixture models used in our study appeared to have overcome these problems. Meanwhile, the OLS model with the combination of variables and interactions showed the best performance, yielding the lowest BIC and RMSE values, yet beyond fit, our choice of the model without interactions was underpinned by the plausibility of utility values across the extremes and the bounded nature of EQ-5D values at a maximum of 1 (i.e., full health) [47].

The PNH CUA model informed by the mapped utilities was based on a Markov cohort framework whereby patients transitioned between three PNH health states representing Hb level at the time of assessment and red blood cell transfusion requirements during the previous four weeks. Together, the health states represented different levels of disease status and impacts on PNH QALYs. A threshold level of 10.5 g/dl, as validated by clinical opinion, captured differences in HRQoL between PNH health states [58]. Based on Tobit model estimations, the utility values were higher for clinically better health states (TA [$Hb \geq 10.5$ g/dl]; mean utility 0.7845) and as such expected to accumulate the greatest HRQoL benefits; patients in the TA state ($Hb < 10.5$ g/dl; mean utility 0.6893) accumulating relatively reduced HRQoL due to anaemia, while patients in the TD health state ($Hb < 10.5$ g/dl; mean utility 0.6439) accumulating the most impaired HRQoL since most of the negative health effects and costs associated with PNH are due to blood transfusions [10].

Some limitations to our study must also be considered, the first being the small sample size of the patient survey (71 individuals) which along with the ultra-rare prevalence of PNH met with the usual barriers of subject recruitment faced in any real-world study. While we have overcome some data shortcomings related to electronically administered surveys, such as built-in prompts to avoid missing data, the survey also relied on self-reporting of clinical data such as Hb level, hence there may have been inaccuracies by patients with recall or other response biases. Moreover, compared with patients from PEGASUS (of which we used data for validating the algorithm; also noting the strict inclusion criteria of the RCT) the external sample of survey patients were clinically heterogeneous; thus, associations observed in the external sample will not be the same as in PEGASUS. While these issues may pose some limitations in generalization, the most optimal analytic approaches were used and the resulting mapping algorithm is thus the best that can be made available given in this small patient sample, a limitation that does not affect diseases with larger and more homogeneous patient samples.

Direct utility mapping is also associated with some limitations. Because the regression models fit to country specific utility scores, calculated on country population-specific value sets, they cannot be used to estimate utilities based on HRQoL data from other countries. Therefore, the entire procedure must be re-run for each country of interest. Although algorithms developed for other disease populations can be adopted, this approach is associated with a risk of bias [47].

Despite limitations inherent to any utility mapping study [59], our selected mapping algorithm showed reliability according to the EQ-5D-3L algorithm by Longworth *et al.* (2014) [1].

Genetic algorithms are powerful analytic tools that can be used to rapidly select best-fitting regression models for estimating health-state utility data that are otherwise unavailable from clinical trials. The PNH EQ-5D-5L direct mapping model estimated using a limited sample size given the rarity of the disease, selected using a genetic algorithm and validated by approaches recommended by HTA agencies [47], enables calculation of reliable health-state utility data required for CUA evaluating treatments of PNH.

Summary points

- EQ-5D-5L data were needed for a French cost–utility analysis of pegcetacoplan, a treatment for adults with paroxysmal nocturnal hemoglobinuria, a rare disease supported with limited data required for clinical and economic evaluations informing health technology assessment submissions.
- Genetic algorithms are powerful analytic tools that can be used to rapidly select best-fitting regression models. Hence, we applied genetic algorithms for ultimately estimating health-state utility data that were otherwise unavailable from the pegcetacoplan clinical trial. Following good practice and reporting guidelines, we mapped European Organization for Research and Treatment of Cancer Quality of Life Questionnaire QLQ-C30 patient-level data collected through a survey in patients with paroxysmal nocturnal hemoglobinuria to their EQ-5D-5L utilities calculated using the EQ-5D-5L French value set.
- The genetic algorithm tested three regression models with and without interaction terms using EQ-5D-5L French utilities as the dependent variable and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire QLQ-C30 domains as independent variables with sex and baseline age as covariates. The selected mapping algorithm showed reliability according to the EQ-5D-3L algorithm by Longworth *et al.* (2014) which is currently recommended by NICE for use in health technology assessment submissions by manufacturers.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://bpl-prod.literatumonline.com/doi/10.57264/cer-2022-0178>

Financial & competing interests disclosure

This study was funded by Apellis Pharmaceuticals, Inc. and Swedish Orphan Biovitrum (SOBI) AB, Stockholm, Sweden. Z Hakimi, K Wilson, J Nazir are employed by SOBI and hold company shares. P Wojciechowski, M Wdowiak were employees of Creativ Ceutical, a consultancy firm, which was commissioned by SOBI to conduct this analysis. J Fishman is an employee of Apellis Pharmaceuticals Inc and holds company shares. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing support, funded by Apellis and guided by the authors, was provided by Gauri Saal, MA Economics, of MEDiSTRAVA, an INIZIO company, London, United Kingdom, and in accordance with International Committee of Medical Journal Editors (ICMJE) (www.icmje.org/icmje-recommendations.pdf) and Good Publication Practice (GPP) guidelines (www.acpjournals.org/doi/10.7326/M22-1460).

Data sharing statement

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of this shared data is in accordance with the terms (if any) agreed upon their receipt. The source of this data is: PEGASUS Trial of pegcetacoplan for paroxysmal nocturnal hemoglobinurea (NCT 04085601).

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