PREDICTING HEALTH UTILITIES FROM PATIENT-REPORTED OUTCOME MEASURES (PROMS) IN RARE DISEASES: A SYSTEMATIC REVIEW OF MAPPING STUDIES

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BACKGROUND

- Patient-reported outcome measures (PROMs) are increasingly used to monitor the progression of rare diseases (RDs) from a patient's perspective [1].
- Disease-specific PROMs seldom provide health state utility values (HSUVs) for cost-effectiveness analyses of novel therapies in RDs.
- Generic preference-based PROMs yielding HSUVs might not be collected in studies on RDs, which affect very small (i.e. less than 1 in every 2000 people in Europe), heterogeneous and geographically dispersed patient populations.
- Mapping allows to obtain HSUVs by establishing a statistical relationship between the two types of instruments:

Source PROM (e.g. LupusQol) → Target PROM (e.g. EuroQol)

OBJECTIVES

- To review systematically all published studies using a mapping approach to derive HSUVs from non-preference-based PROMs in RDs.
- To identify any critical issues in using mapping in RDs and give recommendations for future research.

METHODOLOGY

- This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRSIMA) guidelines [2].
- The following databases were searched without time, study design or language restrictions:
  - ❖ MEDLINE (via PubMed);
  - ❖ the School of Health and Related Research Health Utility Database (ScHARRHUD);
  - ❖ the Health Economics Research Centre (HERC) database of mapping studies (version 7.0) [3].
- The keywords combined terms related to 'mapping' with ORPHANET's list of RD indications* (e.g. '*acromegaly*') [4], besides '*rare*' and '*orphan*'.
- The identified citations were screened independently by two reviewers (MM and AW); any disagreement was solved through discussion with a senior author (MD).
- A predefined, pilot-tested extraction template (in Excel®) was used to collect: *study year, disease, country, study design, sample characteristics, sample size, source and target PROMs, regression techniques, goodness-of-fit measures, adherence to formal guidelines or recommendations*.

*excluding very RDs (<1000 cases documented in medical literature)

RESULTS

- The PRISMA flow diagram displays the process leading to the selection of **25** mapping studies (**Figure 1**), which were split into two groups:
  - ❖ **19** studies developing novel mapping algorithms in RDs (**group A**);
  - ❖ **6** studies applying previous algorithms to RD patient-level data (**group B**).

Figure 1. PRISMA flow diagram

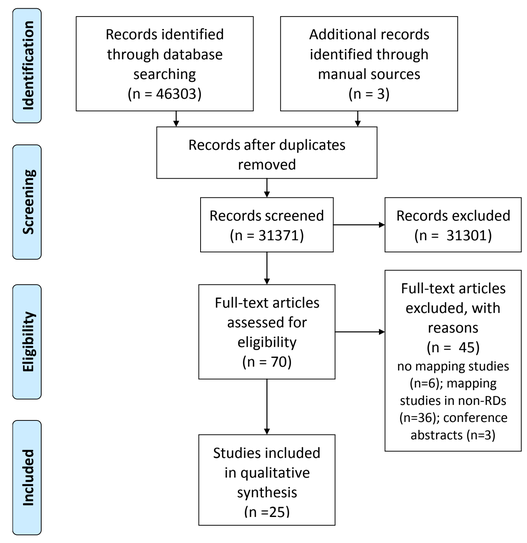

Table 1. List of RDs in included mapping studies (n=25; *group B in colour*).

Cystic fibrosis (n=1)	Epilepsy (n=1)	Multiple myeloma (n=2)	Acromegaly (n=1)	Cushing's syndrome (n=2)
Growth hormone deficiency (n=3)	Peripheral neuropathy (n=1)	Primary sclerosing cholangitis (n=1)	Hereditary angioedema (n=1)	Motor neuron disease* (n=1)
Chronic pain (requiring intraspinal analgesia) (n=1)	Multiple myeloma/ Non-Hodgkin lymphoma (n=1)	Traumatic brain injury (n=1)	Lupus erythematosus (n=2)	Pleural mesothelioma (n=1)
Multiple myeloma/ Non-Hodgkin lymphoma (n=1)	Ovarian cancer (n=2)	Gastroenteropancreatic neuroendocrine tumours (n=1)		Castleman's disease (n=1)

* Motor neuron disease is also known as amyotrophic lateral sclerosis (ALS).

Group A (n=19)

- The studies developed novel mapping algorithms in 14 different RDs (**Table 1**).
- Eleven studies recruited participants from multiple countries.
- As source measure, all studies adopted RD-specific PROMs (e.g. LupusQoL).
- EQ-5D was the target measure in 15 studies; three studies used SF-6D, and one mapped to both EQ-5D and 15D.
- Sample size ranged between 111 and 3437 (median: 401).
- Most studies used Ordinary Least Squares (OLS) regression, although more advanced techniques (e.g., Limited Dependent Variable Mixture Model) were also explored.
- Most studies provided summary measures of fit such as mean error (ME), mean absolute error (MAE), mean squared error (MSE) and root mean squared error (RMSE).
- In general, high levels of error were found at the extremes of the EQ-5D utility scale.
- Only four studies explicitly embraced published recommendations in the field, including the MAPS Statement [5] and ISPOR good practices [6].

Group B (n=6)

- Most studies addressed rare cancers (**Table 1**).
- Five studies were randomized controlled trials (RCTs), and three were intercontinental.
- The studies had three different purposes: **(1)** testing the external validity of existing algorithms in an independent database (n=2); **(2)** identifying the best available algorithms for a specific condition (n=2); **(3)** deriving HSUVs for economic evaluation alongside RCTs (n=2).
- As the original mapping was developed in non-RDs, no RD-specific PROM was used as source measure. Most studies mapped from the EORTC QLQ-C30, a questionnaire widely used in oncology.
- As a target measure, the great majority mapped onto the EQ-5D-3L, one to both EQ-5D-3L and 15D, and one to time trade-off (TTO) utilities.
- Overall, the application of existing algorithms resulted in inaccuracies mainly at the bottom of the EQ-5D scale, since the rare variant of a condition is usually more severe than the condition itself (e.g. pleural mesothelioma *vs*. lung cancer).

Figure 2. Some critical 'issues' around mapping in RDs.

Scarce literature
- Only 25 mapping studies covering 18 different RDs compared to ≈7000 existing RDs
- Relative high number of cancer studies (8/25), especially in group B

Small samples
- 13 out of 19 novel mapping studies (group A) recruited less than 1000 patients
- Risk of failure in predicting HSUVs (mainly at the extremes of the EQ-5D scale)

Lack of research in childhood RDs
- No studies addressing paediatric diseases (e.g. neuroblastoma)
- Adult age (18+) among the inclusion criteria in most studies

Limited sensitivity of generic preference-based PROMs

Some items included in disease-specific PROMs (e.g. communication in ALSFRS-R for motor neuron disease) may not influence HSUVs estimates and be removed from mapping models.

Cultural and linguistic intra-country heterogeneity

The geographic heterogeneity often characterizing multi-country (and even multi-continental) studies in RDs may affect HSUVs; for example, in some countries patients are less willing to report anxiety/depression on the EQ-5D. Identifying the best EQ-5D value set is also critical.

DISCUSSION

- This review identified all published studies mapping non-preference-based PROMs onto *any* preference-based ones in RDs (thus, not limiting to EQ-5D as in a previous review [3]).
- A total of 25 studies were included, of which 19 developed novel mapping in RDs and 6 applied existing algorithms to an original RD dataset.
- Future studies might consider the following to address mapping's challenges in RDs:

➢ developing more algorithms to cover a broader range of RDs including the paediatric ones;

➢ pooling data from multiple observations in longitudinal studies to increase the sample size;

➢ assessing the degree of 'overlap' between the 'source' and the 'target' PROMs before doing mapping;

➢ using PROMs with validated translations and possibly showing consistent results across countries;

➢ testing the generalizability of algorithms developed in non-RDs (e.g. HIV) to similar RDs (e.g. AIDS wasting syndrome);

➢ performing extensive sensitivity analyses when using mapped HSUVs in cost-utility models of treatments for RDs.

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DISCLOSURE

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