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# Relationship Between Patient-Reported Outcomes and Clinical Outcomes in Patients With Morquio A Syndrome

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**Abstract**

This cross-sectional analysis assessed the correlation between patient-reported outcomes (PROs) and clinical outcomes in 24 German patients with Morquio A. Clinical outcomes included 6-minute walk test (6MWT), 3-minute stair climb (3MSC) test, and joint range of motion as measures for endurance/mobility, forced vital capacity (FVC) and maximum voluntary ventilation (MVV) as measures for respiratory function, and height as an important manifestation. The PROs included the EuroQoL (EQ) 5D-5L (EQ5D-5L), to measure health-related QoL (HRQoL), and patients' rating of their ability to walk, climb, or breathe. In adults, endurance and pulmonary function measures and height showed strong and statistically significant correlation with the patients' EQ5D-5L (6MWT: $R = .884$, 3MSC test: $R = .852$, FVC: $R = .815$, MVV: $R = .825$, height: $R = .842$). The adult patients' rating of their ability to walk and climb also correlated strongly with 6MWT ($R = .839$) and 3MSC test ($R = .700$) results. Improvements in these clinical outcomes may be robust surrogate parameters of a better EQ5D-5L/HRQoL in patients with Morquio A.

**Keywords**

Morquio A, mucopolysaccharidosis IV, patient-reported outcomes, quality of life, EQ5D-5L, patient's perception, 6MWT, 3MSC test, FVC, maximal voluntary ventilation, mobility, physical endurance, respiratory function tests

## Introduction

Morquio A syndrome, or mucopolysaccharidosis (MPS) IVA (*Online Mendelian Inheritance in Man* [OMIM] 253000), is a rare lysosomal storage disorder inherited in an autosomal recessive fashion. The disease is caused by a deficiency in the enzyme *N*-acetylgalactosamine-6-sulfatase (GALNS) leading to impaired degradation of the glycosaminoglycans (GAGs) chondroitin-6-sulfate (CS) and keratan sulfate (KS)[1] and disruption of the extracellular matrix function. Morquio A is a multisystemic disease including cardiopulmonary manifestations, severe skeletal abnormalities, and compressive myelopathy. The skeletal manifestations are due to excessive deposition of GAGs in cartilage and bone, resulting in stunted growth with short trunk and neck, genu valgum, hip dysplasia, joint hypermobility/laxity, spinal abnormalities, and pectus carinatum.[2-4] Altogether, these manifestations result in impaired endurance, walking ability, and gait.[3] Therefore, many patients with Morquio A will sooner or later need walking aids or a wheelchair to assist with mobility.[2,4] This progressive nature and the involvement of multiple organs result in significantly impaired functional capacity, endurance, and quality of life (QoL) in these patients. Frequent infections, impaired vision or hearing, frequent surgeries, and (joint) pain and/or fatigue further compromise the patient's QoL.[2,4,5]

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As endurance is a measure of the level of effort required to perform an activity, including functional reserves of the cardiovascular, pulmonary, and/or musculoskeletal systems,[6,7] it can be used to gauge functional capacity in disorders with multiple organ system involvement. The 6-minute walk test (6MWT) is a measure of endurance used in a variety of patient populations, including those with moderate to severe heart and lung diseases, neurological disease, musculoskeletal diseases, and other MPS disorders.[8]

Industry, clinicians, and regulatory authorities increasingly recognize the role of patient-reported measures of health-related QoL (HRQoL) in the evaluation of new therapies and strategies.[9-11] Strong correlations were found between endurance and pulmonary function measures and the patients' HRQoL in different disease areas such as cardiovascular,[12] pulmonary,[13] and musculoskeletal diseases.[14] This suggests that better clinical outcomes will possibly lead to corresponding better results in the patient's HRQoL.

There are currently limited data on how Morquio A affects a patient's HRQoL. One recent study, the patient-reported outcomes (PRO) survey, evaluated the global burden of disease among patients with Morquio A, underscoring mobility (not becoming fully dependent on a wheelchair) as the most important determinant for HRQoL.[15] However, as far as we are aware, no studies have formally assessed the relationship between PRO and clinical outcomes in patients with Morquio A. The aim of this study was therefore to determine the correlation between PRO and clinical outcomes in a German cohort. We also examined whether these relationships are consistent in children (<18 years) as well as in adult (≥18 years) patients with Morquio A.

## Methods

### Study Design and Patient Selection

This cross-sectional analysis included the German patients who participated in the global burden of disease PRO survey in patients with Morquio A as described earlier[15]; as such the PRO data were obtained from the PRO survey database. The clinical outcomes data of these patients were obtained from the Mainz Clinical database and for some patients from the Morquio Clinical Assessment Program (MorCAP) natural history study database.[2] Only German patients were included in the analysis because only for these patients clinical outcomes data were available within a 6-month time window of the PRO survey.

The Morquio A burden of disease survey in Germany was a voluntary, single-assessment, cross-sectional, paper-based survey administered in person via trusted local clinicians. The study population consisted of patients with Morquio A having a confirmed diagnosis of MPS IVA, based on genetic testing or reduced GALNS activity. Eligible patients had to be ≥7 years of age (some exceptions were made due to the limited number of patients) and able to speak, write, and understand their language. Ethics approval was obtained and all patients (or their caregivers) signed an informed consent/ascent form. Additional details have been described previously.[15]

### Patient-Reported Outcomes

In the PRO survey, HRQoL was assessed using the General Health-Related Quality of Life EuroQoL(EQ) 5D-5L questionnaire.[16] This is a generic standardized measure of health status developed by the EuroQoL group and applicable to a wide range of health conditions and therapies. It comprises 5 dimensions (5D), namely, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels (5L) coded from 1 to 5, namely, no problems (1), slight problems (2), moderate problems (3), severe problems and unable to function (mobility, self-care, and usual activities; 4), or extreme problems (pain/discomfort and anxiety/depression; 5), generating a total of 3125 combinations representing different health states. These EQ5D-5L health states can be converted into a single summary index value (utility) by applying a formula that essentially attaches weights to each of the levels in each dimension. This formula is based on the valuation of EQ-5D health states from general population samples.[16] An EQ5D-5L utility value of "1" represents perfect health; a value of "0" represents death. Subsequent normalization to a healthy population can provide negative values indicating that the patient is feeling worse than death.

Next to EQ5D-5L, PROs included the following anchor questions: patient's perception of the ability/strength to walk and climb stairs and the ability to breathe. These anchor questions were developed in a patient focus group to assess the minimal important difference perceptible to patients in the 6MWT, 3-minute stair-climb (3MSC) test, and pulmonary function tests, respectively. The strength to walk (long distances) or to climb stairs was rated from 1 (no strength, unable to walk without mobility aids or paralyzed) to 5 (a great deal of strength) with 2 implying minimal strength, 3 moderate strength, and 4 a good deal of strength. The ability to breathe was rated from 1 (very low) to 5 (very high).

### Clinical Outcomes

Endurance/mobility was evaluated using the 6MWT (ATS statement 2002) and the 3MSC test.[17] Respiratory function was investigated by measuring forced vital capacity (FVC)[18] and maximum voluntary ventilation (MVV)[18] during spirometry. In addition, the following joint range of motion (ROM) tests were measured using a double-armed goniometer as described previously[19,20]: hip extension, wrist extension, and shoulder flexion. Since the range of active shoulder flexion may be influenced by spinal retroflexion, the test was done in the thorax plane rather than in the vertical plane. Hip extension was scored against normal. Shoulder flexion and wrist extension were expressed as actual values.

### Statistical Analysis

The correlation between the PRO data from the Morquio A global burden of disease survey and the clinical outcomes data from the Mainz Clinical or MorCAP natural history databases

was assessed using analysis of variance regression analysis providing Pearson's coefficients ($R$), slopes as well as coefficients of determination (adjusted $R^2$). $R$ values >.7 were considered to demonstrate strong correlation; $P$ values <.05 were considered statistically significant. Clinical outcome data obtained outside a 6-month time window from the PRO data were ruled out for analysis.

## Results

### Patient Characteristics

The analysis involved 24 German patients with Morquio A (14 adults aged ≥18 years and 10 children aged 10-17 years). Demographics and clinical characteristics of the participants are shown in Table 1. In all patients, the height varied between 94 and 170 cm with a mean height of 121.3 cm (123.9 cm in adults and 117.9 cm in children). The EQ5D-5L utility score varied between −.205 and 1 in all patients with a mean utility score of .552 (.422 in adults and .763 in children). In all patients, the 6MWT distance ranged from 0 (not able to walk) to 531.7 m with a mean of 212.9 m (131.3 m in adults and 317.8 m in children). For the 3MSC test, the results varied between 0 (not able to climb stairs) and 206 stairs with a mean of 106.1 stairs (72.0 stairs in adults and 140.3 stairs in children). Regarding the pulmonary function parameters in all patients, the mean FVC was 1.9 L and the mean MVV was 46.6 L/min.

### Correlation Between Endurance and Pulmonary Function Measures and Height With HRQoL/EQ5D-5L

Table 2 shows the correlation between endurance and pulmonary function measures and height with the EQ5D-5L utility score in all patients with Morquio A and split for adults and children.

A strong and statistically significant correlation was found between the 2 endurance parameters and the EQ5D-5L utility score in all patients: $R = .713$ ($P = .0019$) and $R = .693$ ($P = .0060$) for the correlation with the 6MWT and 3MSC test, respectively. For FVC and MVV, a moderate but statistically significant correlation with the EQ5D-5L utility score was shown in all patients: $R = .521$ ($P = .0155$) and $R = .534$ ($P = .0126$), respectively.

Strongest (and statistically significant) correlations were observed in adult patients, whereas only poor correlations were observed in children (Table 2). In adult patients, the Pearson's coefficient $R$ between the endurance measures and the QoL utility score was .884 for the 6MWT ($P = .0016$; Supplementary Figure 1a) and .852 for the 3MSC test ($P = .0149$; Supplementary Figure 1b). For pulmonary function measures, the Pearson's coefficient $R$ was .815 for the FVC ($P = .0007$; Supplementary Figure 1c) and .825 for the MVV ($P = .0005$; Supplementary Figure 1d). Regression analysis indicated that the 6MWT was most closely associated with EQ5D-5L (Supplementary Figure 1a). An increase of 100 m in the 6MWT distance was associated with a .2 increase in the EQ5D-5L utility score. This is consistent with the highest correlation found between the 6MWT and EQ5D-5L score.

A moderate but statistically significant correlation was also observed between height and EQ5D-5L utility score in all patients: $R = .477$ ($P = .0289$). In line with the results for

**Table 1.** Patient Demographics and Clinical Characteristics.

| | All Patients | Adult | Children |
|---|---|---|---|
| N | 24 | 14 | 10 |
| Age in years, N (%) | | | |
| 10-14 | 8 (33.3) | 0 | 8 (80) |
| 15-17 | 2 (8.3) | 0 | 2 (20) |
| 18-24 | 9 (37.5) | 9 (64.3) | 0 |
| 25-29 | 2 (8.3) | 2 (14.3) | 0 |
| 40-44 | 1 (4.2) | 1 (7.1) | 0 |
| 45-49 | 1 (4.2) | 1 (7.1) | 0 |
| 50-54 | 1 (4.2) | 1 (7.1) | 0 |
| Gender, N (%) | | | |
| Male | 16 (66.7) | 11 (78.6) | 5 (50) |
| Female | 8 (33.3) | 3 (21.4) | 5 (50) |
| Height in cm | | | |
| N | 23 | 13 | 10 |
| Mean (SD) | 121.3 (22.9) | 123.9 (22.1) | 117.9 (24.7) |
| Range | 94-170 | 96-170 | 94-156[a] |
| EQ5D-5L (HRQoL) | | | |
| N | 21 | 13 | 8 |
| Mean (SD) | .552 (.342) | .422 (.363) | .763 (.160) |
| Range | -.205-1.000 | -.205-.828 | .493-1.000 |
| 6MWTD, m | | | |
| N | 16 | 9 | 7 |
| Mean (SD) | 212.9 (179.9) | 131.3 (162.1) | 317.8 (151.9) |
| Range | 0.0-531.7 | 0.0-373.3 | 65.9-531.7 |
| 3MSC, # stairs | | | |
| N | 14 | 7 | 7 |
| Mean (SD) | 106.1 (77.4) | 72.0 (80.6) | 140.3 (61.5) |
| Range | 0-206 | 0-206 | 25-206 |
| FVC, L | | | |
| N | 21 | 13 | 8 |
| Mean (SD) | 1.9 (1.4) | 1.9 (1.4) | 1.8 (1.4) |
| Range | .5-4.7 | .5-4.7 | .5-4.5 |
| MVV, L/min | | | |
| N | 21 | 13 | 8 |
| Mean (SD) | 46.6 (39.9) | 52.7 (47.8) | 36.8 (21.3) |
| Range | 0.0-138.9 | 0.0-138.9 | 14.2-71.8 |
| Wrist extension | | | |
| N | 12 | 8 | 4 |
| Mean (SD) | 85.8 (23.5) | 78.6 (25.3) | 100 (10.8) |
| Range | 50-120 | 50-120 | 90-115 |
| Shoulder flexion | | | |
| N | 11 | 7 | 4 |
| Mean (SD) | 138.0 (19.9) | 133.7 (24.2) | 145.5 (5.3) |
| Range | 96-170 | 96-170 | 140-150 |
| Hip extension | | | |
| N | 12 | 7 | 5 |
| Mean (SD) | −18.4 (8.1) | −20.6 (7.8) | −15.4 (8.4) |
| Range | -30 - -5 | -30 - -5 | -30 - -10 |

Abbreviations: 3MSC, 3-minute stair climb test; 6MWTD, 6-minute walk test distance; EQ5D-5L QoL, EuroQoL-5 dimensions-5 levels; FVC, forced vital capacity; HRQoL, health-related quality of life; MVV, maximum voluntary ventilation; SD, standard deviation.

[a]156 cm: male in the 15 to 17 years age category.

**Table 2.** Pearson's Correlation and Regression Analysis Between Endurance and Pulmonary Function Measures and Height and the Patient's EQ5D-5L/Health-Related Quality of Life.

| PRO Measure | Clinical Measure | Number of Patients | Pearsons's Coefficient ($R$) | Slope | Coefficient of Determination (Adjusted $R^2$) | Significance |
|---|---|---|---|---|---|---|
| EQ5D-5L HRQoL: all patients | 6MWT | 16 | .713 | .001 | .508 | .0019 |
| | 3MSC | 14 | .693 | .003 | .437 | .0060 |
| | FVC | 21 | .521 | .128 | .233 | .0155 |
| | MVV | 21 | .534 | .0046 | .248 | .0126 |
| | Height | 21 | .477 | .007 | .186 | .0289 |
| EQ5D-5L HRQoL: adults | 6MWT | 9 | .884 | .002 | .750 | .0016 |
| | 3MSC | 7 | .852 | .003 | .671 | .0149 |
| | FVC | 13 | .815 | .205 | .633 | .0007 |
| | MVV | 13 | .825 | .006 | .652 | .0005 |
| | Height | 13 | .842 | .014 | .682 | .0003 |
| EQ5D-5L HRQoL: children | 6MWT | 7 | .212 | −.0002 | −.146 | .2362 |
| | 3MSC | 7 | .008 | −.00002 | −.200 | .9870 |
| | FVC | 8 | .098 | .0113 | −.155 | .8172 |
| | MVV | 8 | .042 | .0003 | −.165 | .9216 |
| | Height | 8 | .124 | .0007 | −.149 | .7702 |

Abbreviations: 3MSC, 3-minute stair climb test; 6MWT, 6-minute walk test; EQ5D-5L QoL, EuroQoL-5 dimensions-5 levels; HRQoL, health-related quality of life; FVC, forced vital capacity; MVV, maximum voluntary ventilation; PRO, patient-reported outcome.

**Table 3.** Pearson's Correlation and Regression Analysis Between Skeletal Flex Extensions and the Patient's EQ5D-5L/Health-Related Quality of Life.

| Patient Group | PRO Measure | Clinical Measure | N | Pearson's Coefficient ($R$) | Slope | Coefficient of Determination (Adjusted $R^2$) | Significance |
|---|---|---|---|---|---|---|---|
| All patients | EQ5D-5L HRQoL | Wrist extension | 12 | .011 | −.0001 | −.099 | .9739 |
| | | Shoulder flexion | 11 | .182 | −.003 | −.074 | .5931 |
| | | Hip extension | 11 | .511 | .021 | .187 | .0895 |
| Adults | EQ5D-5L HRQoL | Wrist extension | 8 | .360 | −.005 | −.016 | .3812 |
| | | Shoulder flexion | 7 | .348 | −.005 | −.054 | .4439 |
| | | Hip extension | 7 | .565 | .027 | .183 | .1866 |
| Children | EQ5D-5L HRQoL | Wrist extension | 4 | .841 | .013 | .561 | .1589 |
| | | Shoulder flexion | 4 | .943 | −.031 | .835 | .0566 |
| | | Hip extension | 5 | .123 | .002 | −.313 | .8441 |

Abbreviations: EQ5D-5L QoL: EuroQoL-5 dimensions-5 levels; HRQoL: health-related quality of life; PRO: patient-reported outcome.

endurance and pulmonary function measures, the correlation was strong and statistically significant in adult patients and poor and non-statistically significant in children: $R = .842$ ($P = .0003$) and $R = .124$ ($P = .7702$), respectively (Table 2).

## *Correlation Between Skeletal Flex Extensions and HRQoL/EQ5D-5L*

The correlation and regression between flex extension tests of different joints and the EQ5D-5L utility score were also determined (Table 3). In all patients with Morquio A, none of the flex extension tests correlated statistically significantly with the EQ5D-5L utility score. Moderate correlation ($R = .511$, $P = .0895$) was observed between the EQ5D-5L utility score and hip extension, whereas the correlation with wrist extension and shoulder flexion was poor: $R = .011$ and $R = .182$, respectively. The same pattern was shown in adult patients: poor and nonsignificant correlation between EQ5D-5L and wrist extension and shoulder flexion ($R = .360$ with $P = .3812$ and $R = .348$ with $P = .4439$, respectively), whereas hip extension correlated moderately but not statistically significantly with EQ5D-5L ($R = .565$ with $P = .1866$). In children, the correlation pattern was opposite. Wrist extension and shoulder flexion correlated strongly (though probably due to small sample size not significantly) with the EQ5D-5L utility score ($R = .841$ with $P = .1589$ and $R = .943$ with $P = .0566$, respectively). However, only poor correlation was shown between hip extension and the EQ5D-5L utility score ($R = .123$; Table 3).

## *Correlation Between Patient's Perception and Endurance and Pulmonary Function Measures*

Finally, the correlation and regression fit between the patient's perception ratings to perform a specific task and the endurance (6MWT and 3MSC test; Figure 1) and pulmonary

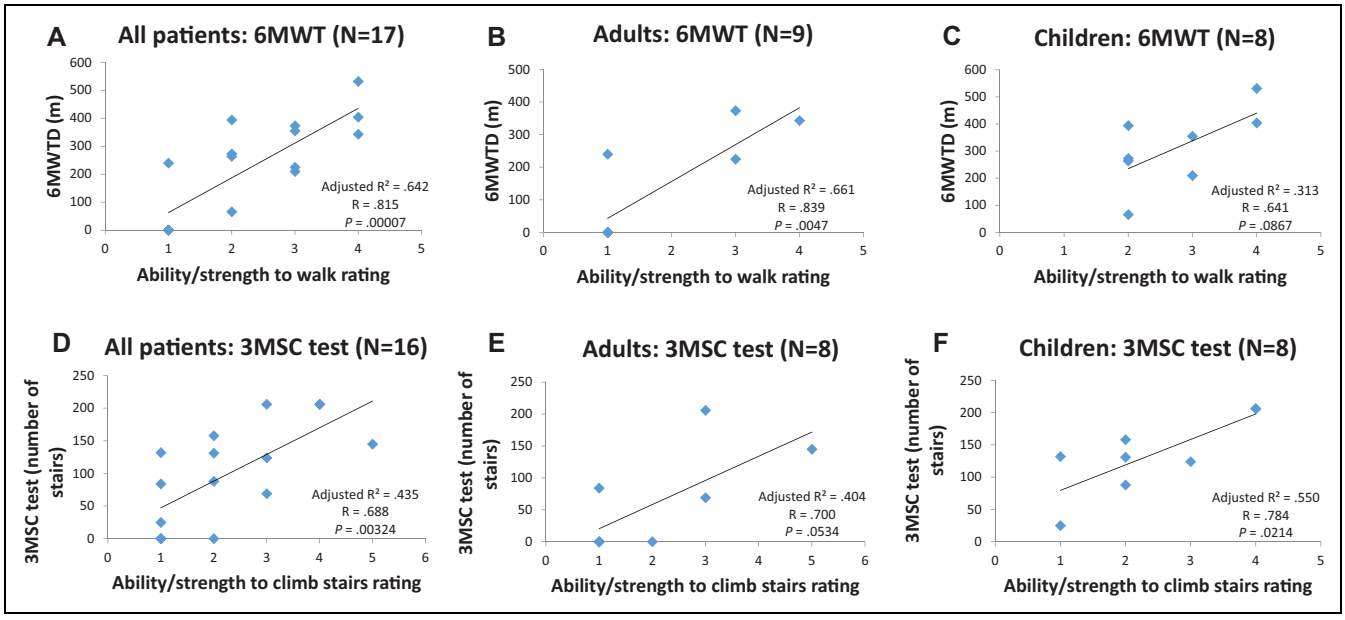


**Figure 1.** Pearson's correlation and regression analysis between endurance measures and the patient's perception of the ability/strength to walk or climb stairs in patients with Morquio A. 6MWT versus ability/strength to walk in (A) all patients, (B) adults, and (C) children; 3MSC test versus ability/strength to climb stairs in (D) all patients, (E) adults, and (F) children. The solid lines represent predicted regression lines between the patient's perception scores and endurance measures. Please note that data from all patients may not be visible due to overlap of some data points (eg, 4 adult patients with a 6MWTD of 0 m rated their ability/strength to walk as 1, that is, no strength/unable to walk without mobility aids or paralyzed). Abbreviations: 6MWT(D), 6-minute walk test (distance); 3MSC, 3-minute stair climb test; *R*, Pearson's coefficient; Adjusted $R^2$, coefficient of determination; ANOVA, analysis of variance. *P* value determined by ANOVA test. The patient's perception was scored using values ranging from 1 to 5 with 1 = no strength (or unable to perform the task or paralyzed), 2 = minimal strength, 3 = moderate strength, 4 = a good deal of strength, and 5 = a great deal of strength.

function (FVC and MVV; Supplementary Table 1) measures was determined.

In all patients with Morquio A, a strong and statistically significant correlation was observed between both the patient's perception of their ability/strength to walk and the 6MWT (N = 17, $R = .815$, $P = .00007$; Figure 1A) and the patient's perception of their ability/strength to climb stairs and the 3MSC test (N = 16, $R = .688$, $P = .00324$; Figure 1D). This was confirmed in adults and children. For the 6MWT results, the Pearson's coefficient *R* was .839 and .641 for adults (Figure 1B) and children (Figure 1C), respectively. This was statistically significant in adults ($P = .0047$) and approached significance in children ($P = .0867$). For the 3MSC test results, the Pearson's coefficient *R* was .700 and .784 for adults (Figure 1E) and children (Figure 1F), respectively. This was statistically significant ($P = .0214$) in children and approached significance in adults ($P = .0534$).

In contrast with the results for endurance measures, only a moderate to poor and non-significant correlation was found between the pulmonary function test (FVC and MVV) results and the patient's perception of the ability to breathe (Supplementary Table 1). In all patients with Morquio A, Pearson's coefficients were .318 and .164 for FVC and MVV, respectively. Similar results were obtained in both age subgroups.

In addition to the correlation, the regression fit analysis was assessed for the clinical outcomes and the patient's perception (Figure 1 and Supplementary Table 1). Best fit result was observed between the 6MWT and the adults' perception of walking ability, which is in line with the result in the previous section (6MWT vs EQ5D-5L; Figure 1B).

## Discussion

In this article, we evaluated the relationship between PRO from the Morquio A PRO global burden of disease study[15] and clinical outcomes from the Mainz Clinical database and the MorCAP database.[2] Mean values showed impaired endurance and pulmonary function, markedly below that documented for healthy participants.[21–23] *R* values >.7 and *P* values <.05 show that height as well as endurance (6MWT and 3MSC test) and pulmonary function measures (FVC and MVV) have excellent correlation with EQ5D-5L in Morquio A, mainly in adult patients. This indicates that better results in clinical outcomes such as height, the 6MWT, 3MSC test, FVC, and MVV are likely to be associated with better EQ5D-5L/HRQoL in the patient. Only poor correlation was observed in children. This might be explained by large differences in disease progression in these young patients resulting in a very heterogeneous group with varying results.

Reduced height is regarded as one of the phenotypical characteristics of Morquio A. This was confirmed by impaired mean values of 123.9 cm in adults and 117.9 cm in children aged 10 to 17 years observed in our German patients, which are in line with previously published data in these age categories.[24]

However, a big variability in height range was observed up to a value of 170 cm in adults and 156 cm in a male child in the 15- to 17-year age category (which was still within the 97$^{th}$ centile of previously published growth charts for male patients with Morquio A[24]). This variability in height range can possibly be explained by heterogeneity in disease phenotype. Height is (sometimes) considered to be related to mortality, to the aggressiveness of the disease, and therefore a reduced HRQoL. Our analysis shows that height does indeed seem to be correlated with the EQ5D-5L/HRQoL.

The results from our analysis are in line with studies in other disease areas.[12,13,14,25,26] In patients with heart failure, FVC and MVV were shown to be predictors for QoL.[12] In patients with Duchenne muscular dystrophy, strong correlation was observed between the 6MWT and the Pediatric Outcomes Data Collection Instrument domain score for transfer and basic mobility ($R = .79$).[14] Likewise, QoL was correlated with the 6MWT in pulmonary disorders[13,25,26] and with FVC in patients who underwent a pulmonary resection due to lung cancer.[13]

We also examined the correlation between the ROM of various joints (hip, wrist, and shoulder) and the patient's EQ5D-5L. In all patients with Morquio A, none of the flex extension tests correlated strongly or statistically significantly with the patient's EQ5D-5L. However, hip extension correlated moderately ($R = .511$) with EQ5D-5L ($P = .0895$). The same patterns were found in adult patients. In contrast, children showed stronger correlation between wrist extension and shoulder flexion and EQ5D-5L. This might be explained by the involvement of the hip joint in mobility, which is possibly of greater importance for adult patients. On the other hand activities that include wrist and shoulder movements, such as writing and playing, seem to be key determinants for children's EQ5D-5L. Alternatively, this result could reflect the relevance of these joints in terms of being able to use mobility aids (such as crutches).

In addition to the correlation with the EQ5D-5L utility scores, we also evaluated the correlation between the clinical outcomes and the patient's perception to perform a specific task (walk or climb stairs). In line with the results for EQ5D-5L, a good to strong correlation was also found between the 6MWT and 3MSC test results and the patients' rating of their ability/strength to walk and climb stairs. This (statistically significant) result was observed in all patients with Morquio A ($P = .00007$ for 6MWT; $P = .00324$ for 3MSC test correlation) as well as in adults ($P = .0047$ for 6MWT; $P = .0534$ for 3MSC test correlation) and children ($P = .0214$ for 3MSC test; $P = .0867$ for 6MWT correlation) separately, indicating that gains in these endurance outcomes are perceptible for all patients and translate into increased mobility. It should be noted that the correlation with the 3MSC test in adults and with the 6MWT in children may not have reached statistical significance because of the small patient numbers involved in the age subgroup analyses. Although both adults and children displayed a strong correlation between the 3MSC test and the ability to climb stairs, this relationship was even more prominent in children. This might be explained by the fact that improvements in the 3MSC test might be smaller in adult patients, possibly due to progressive skeletal damage leading to difficulties in climbing stairs.[2,5] This is underscored by the difference in mean values between children and adults for the 3MSC test results. In adult patients with Morquio A, the mean number of stairs climbed during the 3MSC test was 72, whereas it was 140 stairs in children. Moreover, the mean EQ5D-5L utility scores/HRQoL were higher for children (.763) compared to adults (.422), which might be explained by a less advanced disease and less wheelchair use in children.[15]

In contrast to the strong correlations between endurance measures and the perception of patients how well they could walk or climb stairs, patients seem to have difficulties in effectively rating their pulmonary function. The poor correlation between the patients' rating of their ability to breathe and the MVV and FVC readings indicates that changes in pulmonary function might not be perceptible by patients with Morquio A. This is in line with other PRO studies showing poor ability of patients to rate their lung function capacity,[27] underlining the importance of dyspnea rating scales in patients with impaired lung function.[28] Correlation between pulmonary function measures and the self-rated breathing ability was also greater in children than in adults. Again, this might be explained by the more advanced disease stage in adult patients with Morquio A leading to increased difficulty in breathing.[5] Possibly, this should also be regarded in the light of the limited number of patients and large standard deviation.

Overall, our results show strong correlations in adult patients with Morquio A for measures that reflect the patient's endurance/mobility: the 6MWT and the 3MSC test versus EQ5D-5L and the patient's rating of their ability/strength to walk and climb stairs. Also, hip extension showed a good correlation with EQ5D-5L. Altogether the strong correlation with these mobility measures further supports the importance of mobility for the patient's EQ5D-5L/HRQoL. This is in line with recently published data by Hendriksz CJ et al, pinpointing mobility as the key determinant for HRQoL in patients with Morquio A.[15] The authors showed that HRQoL reduces dramatically if patients become always wheelchair dependent and that even a slight increase in mobility (wheelchair use only when needed) greatly improves HRQoL. Therefore, increased mobility will likely translate into greater independence and would lead to less dependence on caregivers for care and support in undertaking activities of daily living.[29] However, greater mobility might not necessarily translate into improved independence in children as most children are not considered independent and require caregivers regardless of mobility level.[15] This might explain why there was a poor correlation between the endurance measures and pulmonary function tests with EQ5D-5L in children with Morquio A. Furthermore, the heterogeneity in this group further complicates the analysis and interpretation of these results.

It should be taken into account that only a small number of patients were included in this study (inherent to the ultra-rare nature of this disease) and that information was missing for

some patients. Moreover, longitudinal data from a larger, international patient group are essential to confirm the findings from this cross-sectional analysis and would be the goal of future studies and publications. Validation of these findings would strengthen the value of the impact of changes in these measures on the patient's HRQoL.

## Conclusion

Strong correlations were observed between HRQoL, as measured by the EQ5D-5L, with endurance and pulmonary function measures and height in patients with Morquio A, in particular in adult patients. Also, the patient's perception of the ability to walk or climb stairs correlated very well with the 6MWT and 3MSC test, independent of age. Therefore, increases in endurance and pulmonary function measures and height are likely to be associated with perceptible gains in mobility and/or HRQoL in patients with Morquio A.

### Authors' Note

All procedures followed were in accordance with the Ethics Committee of Rheinland Palatinate and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent for being included in the study was obtained from all patients.

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### Supplemental Material

The online data supplements are available at http://iem.sagepub.com/supplemental

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