Characterizing Most Bothersome Symptom and Minimal Clinically Important Difference to Establish Patient-Relevant

Endpoints in Fabry Disease

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BACKGROUND

- Fabry disease (FD) is a rare genetic disorder caused by a deficiency of a lysosomal enzyme,
 a-galactosidase-A, with a multisystemic symptom presentation.¹
- The systematic collection of disease-specific symptoms and their impact on the lives of patients with FD can offer unique insights into the patient experience.

The Fabry Disease-Patient Reported Outcome (FD-PRO) is a psychometrically validated instrument that assesses the severity of FD symptoms in adults

- O It consists of 19 items that measure neuropathic symptoms (pain, tingling, numbness, and burning in upper/lower extremities), headache, abdominal pain, heat intolerance, swelling, tinnitus, fatigue, hearing/vision impairment, hypohidrosis, and difficulty engaging in regular physical activities.^{1, 2}
- The symptom severity of each FD-PRO item is evaluated on a 0 (no symptom) to 10 (symptom at its worst) numeric rating scale (NRS) with a recall period of the past 24 hours.^{1, 2}

OBJECTIVE

- To characterize the most bothersome symptoms (MBS) in FD and assess the severity of MBS using the FD-PRO instrument.
- To quantify the meaningful improvement in symptoms as perceived by patients and estimate Minimal Clinically Important Difference (MCID) a useful metric to personalize patient-relevant endpoints using the FD-PRO.

METHODS

- Adult patients with FD (n=66) were recruited in an online cross-sectional survey through Fabry Support & Information Group.
- US-based Fabry adults (18 and older) who experienced neuropathic and abdominal pain were eligible for participating in this study. Participants completed the FD-PRO, identified the three MBS, and estimated their perceived meaningful improvement in the MBS [hereafter referred to as minimal clinically important difference (MCID)].
- Participants were asked to identify their top three MBS from a list of symptoms assessed in the FD-PRO and an option for "other symptom". Due to small sample sizes, reporting of MBS is a combination of the symptoms reported as first, second, or third most bothersome.

RESULTS

Demographic details and pain ranking of responders

- Respondents were predominantly middle-aged (mean age of 44.0 years), female (59%), with the classic phenotype (65.2%), and the mean time since FD diagnosis was 14.2 years.
- Participants mostly reported moderate or severe neuropathic pain (77.3%) and gastrointestinal pain (65.1%). Self-reported clinical characteristics are reported in **Table 1**

Table 1: Respondent-reported demographic and clinical characteristics

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Characteristics (N=66) ¹		Statistics
Age (Years), Mean (SD)		44.0 (12.7)
Female		39 (59.1%)
Time since FD diagnosis, Mean (SD) (n=64)		14.2 (11.2)
eGFR value, Mean (SD) (n=26)		67.9 (33.1)
FD phenotype (n=60)		
Classic		43 (65.2%)
Non-classic (Late Onset)		17 (25.8%)
Comorbidities (n=65)		
At least one comorbidity		32 (48.5%)
Non-cardiovascular comorbidities		33 (50.0%)
Treatment Status		
Untreated		9 (13.6%)
Treated		57 (86.4%)
Pain Severity Ranking ²	Neuropathic Pain – n (%)	Gastrointestinal Pain - n (%)
Very severe	7 (10.6%)	6 (9.1%)
Severe	25 (37.9%)	20 (30.3%)
Moderate	26 (39.4%)	23 (34.8%)
Mild	8 (12.1%)	12 (18.2%)
No pain	0 (0.0%)	5 (7.6%)

eGFR estimated Glomerular Filtration Rate; FD, Fabry disease; n, number of patients; SD, standard deviation ¹Response is reported out of 66 patients unless otherwise indicated.

²Severity of the neuropathic pain (pain in the feet, legs, hands, and/or arms) and gastrointestinal pain (stomach and/or intestinal area) were assessed as screening questions during the FD patient experience survey on a 1 (very severe) to 6 (don't know/prefer not to answer) rating scale.

Pain profile of respondents

- For pain frequency, most respondents reported experiencing neuropathic pain episodes several times per day in the upper extremities (hands or arms, 34.8%) and lower extremities (feet and legs, 43.9%); abdominal pain was mainly reported a few times a week (31.8%).
- Respondents mainly reported neuropathic pain crises in the upper extremities (66.7%, n=30) and lower extremities (80.0%, n=36) and pain crisis in the abdomen (51.1%, n=23).

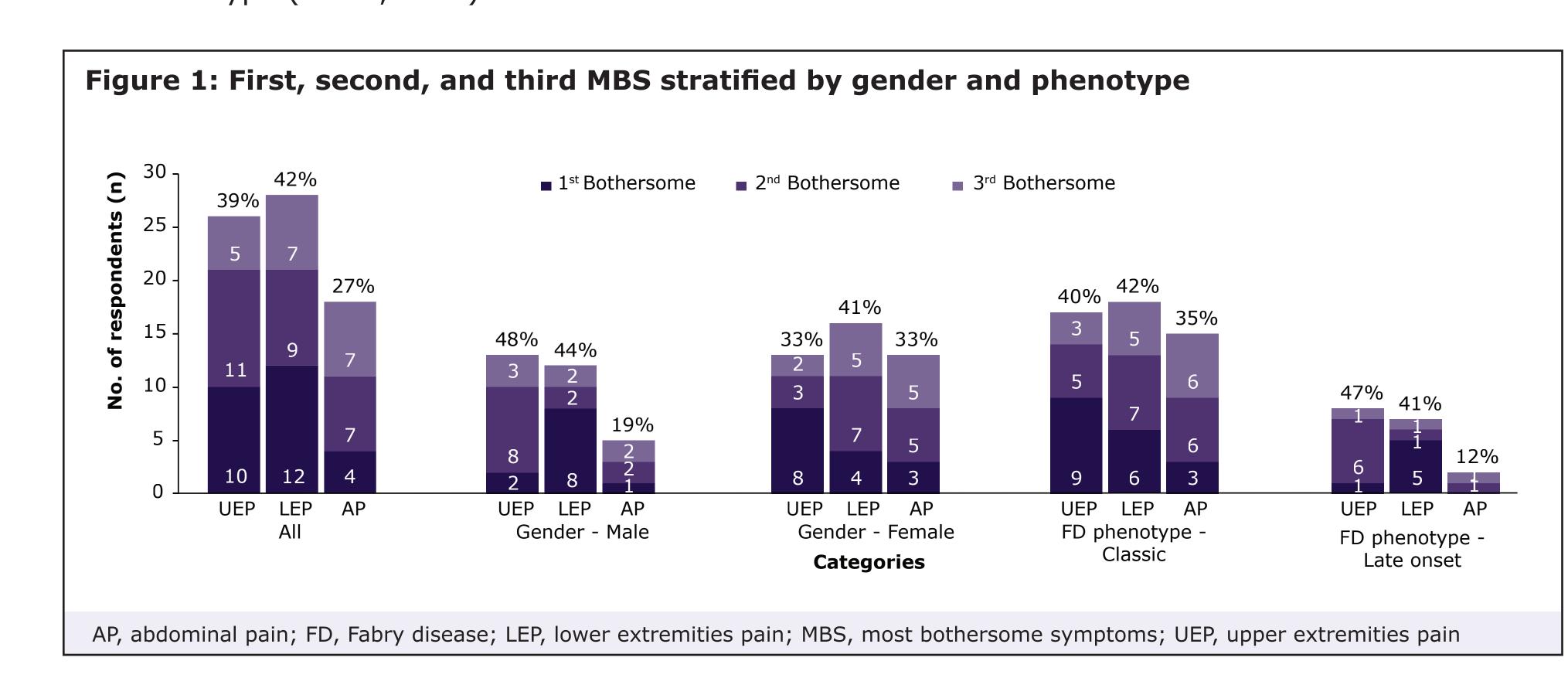
Most Bothersome Symptoms (MBS)

- Overall, participants reported neuropathic pain in lower extremities (42.4%; median severity: 7.0; interquartile range (IQR), Q1-Q3: 4.5-9.0) and upper extremities (39.4%; median severity: 6.5; IQR: 5.0-7.0), and abdominal pain (27.3%; median severity: 5.5; IQR: 4.0-8.0) as most commonly reported MBS (**Figure 1**).
 - Of participants reporting neuropathic pain in upper extremities, ten (38.5%) reported it as 1^{st} MBS, 11 (42.3%) respondents it as a 2^{nd} MBS, and five (19.2%) respondents as a 3^{rd} MBS.
- O Neuropathic pain in lower extremities was 1st MBS for 12 (42.9%), 2nd MBS for nine (32.1%), and 3rd MBS for seven (25.0%) for respondents who reported experiencing this symptom.
- O In patients who experienced abdominal pain, four (22.2%) reported it as the 1st MBS, whereas seven (38.9%) respondents each reported it as 2nd and 3rd MBS (**Figure 1**).

MBS across respondents stratified by gender and FD phenotype

When stratified by gender, a greater proportion of males characterized neuropathic pain in upper extremities as an MBS (n=13, 48%), while a greater proportion of females characterized neuropathic pain in lower extremities as an MBS (n=16, 41%, **Figure 1**).

- When stratified by Fabry phenotype, neuropathic pain in lower extremities as an MBS was more pronounced in classic type (n=18, 42%), and neuropathic pain in upper extremities as an MBS was more pronounced in late-onset type (n=8, 47%, **Figure 1**).
- Abdominal pain was more frequently reported as an MBS in female respondents (n=13, 33%) and classic type (n=15, 35%).



Estimated Minimal Clinically Important Difference in FD-PRO symptoms

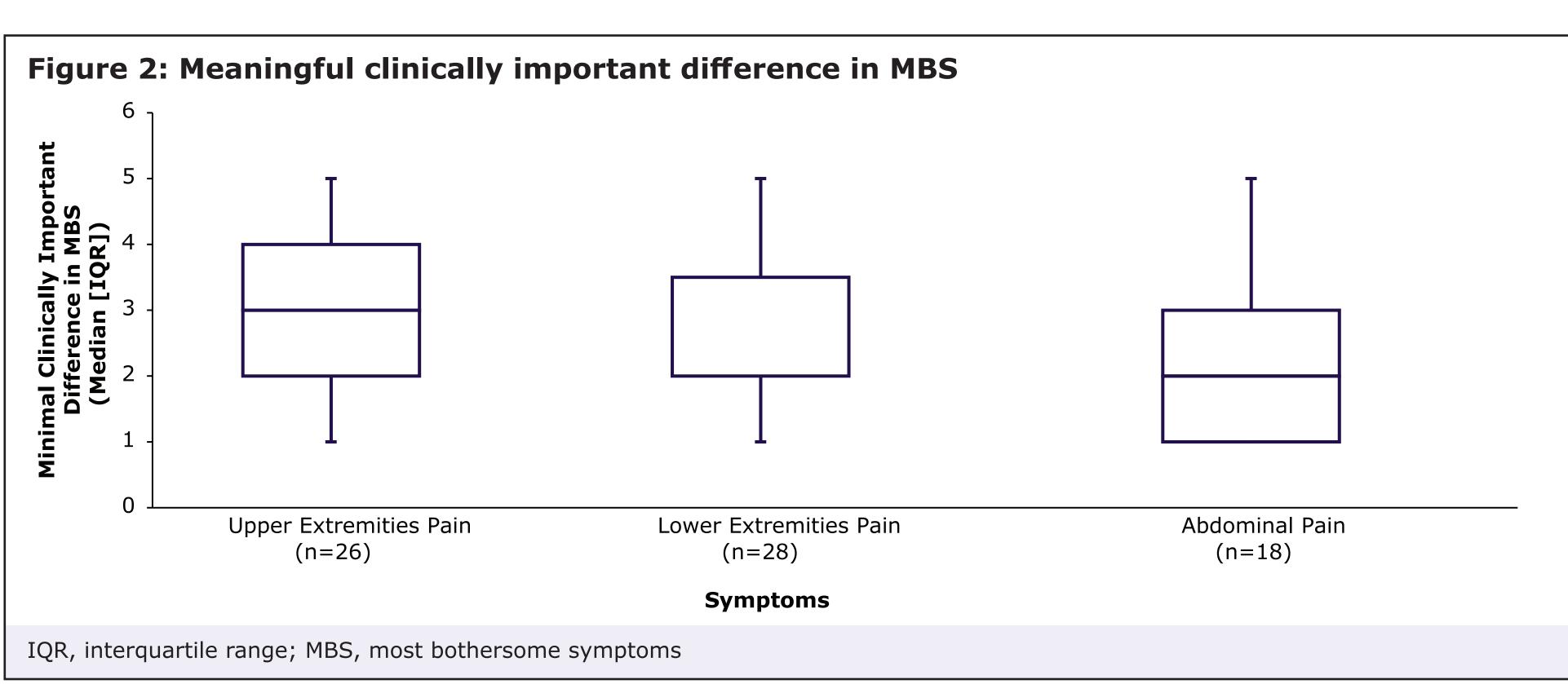
- Among the full sample, respondents reported a perceived meaningful improvement score for neuropathic pain in upper extremities (median severity [IQR]: 3.0 [2.0–4.0]), lower extremities (2.0 [2.0–3.0]) and abdominal pain (2.0 [1.0–3.0] (**Table 2**).
- The median perceived meaningful improvement score ranged between 2 and 3 points, which means that a decrease of 2 to 3 points on the NRS of 0-10 was perceived by respondents to be a meaningful improvement across all symptoms.

Table 2: Meaningful clinically important difference in FD-PRO symptoms

FD-PRO symptoms	The meaningful improvement in FD-PRO symptoms (Median severity [IQR]); N=66	
Pain in your hands or arms	3.0 (2.0-4.0)	
Burning in your hands or arms	2.0 (2.0-3.0)	
Numbness in your hands or arms	2.0 (2.0-3.0)	
Tingling in your hands or arms	2.0 (2.0-3.0)	
Pain in your feet or legs	2.0 (2.0-3.0)	
Burning in your feet or legs	2.5 (2.0-3.0)	
Numbness in your feet or legs	2.0 (1.0-3.0)	
Tingling in your feet or legs	2.0 (1.0-3.0)	
Headache	2.5 (1.0-3.0)	
Abdominal pain (stomach and/or intestinal)	2.0 (1.0-3.0)	
Feeling too hot	3.0 (2.0-4.0)	
Swelling in your legs and feet	2.0 (1.0-3.0)	
Ringing or buzzing in your ear(s)	2.0 (1.0-3.0)	
Feeling tired	3.0 (1.0-3.0)	
Hearing problems	2.0 (1.0-3.0)	
Vision problems	2.0 (1.0-3.0)	
Sweating	2.0 (1.0-3.0)	
Difficulty to engage in regular physical activities	2.0 (1.0-4.0)	
FD-PRO, Fabry Disease-Patient Reported Outcome; IQR, interquartile range		

Estimated Minimal Clinically Important Difference in MBS

- MCID was further assessed in a subset of respondents who reported neuropathic pain in upper extremities (n=26), neuropathic pain in lower extremities (n=28), or abdominal pain (n=18) as bothersome.
- Within this subset of respondents, the median and interquartile range (Q1–Q3) of MCID for MBS was reported as 3.0 (2.0–4.0), 2.0 (2.0–3.5), and 2.0 (1.0–3.0) for neuropathic pain in upper extremities, lower extremities, and abdominal pain, respectively (Figure 2).



CONCLUSIONS

Neuropathic pain in the lower extremities, upper extremities, and abdominal pain were among the top three most bothersome symptoms reported by all respondents.

- A patient-derived minimal clinically important difference for the three most bothersome symptoms
 was reported as IQR between 1 to 4 points on a numeric rating scale of 0 to 10.
- Even among a subset of respondents who noted symptoms as bothersome, the MCID remained between 1 to 3 points.
- The study findings have implications for understanding the heterogeneity and presentation of symptoms in Fabry disease and estimating the minimal clinically important difference of the FD-PRO in clinical studies.
- MCID estimates were based on patient-perceived change, which is one method of evaluating MCID. Additional methods to establish MCID thresholds include distribution- and/or anchor based methods.
- Generalizability of the results outside of the sample tested is unknown.

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CONFLICTS OF INTEREST

NL, JK, IA, and PDM: Sanofi employees and stockholders of the company. IW: On assignment at Sanofi through Artech, LLC. CB and JJ: FSIG employees who provided patient outreach and recruitment. GF: IQVIA employee which received financial support from Sanofi for this

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