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Patient and caregiver burden of neuronopathic Gaucher disease: The GARDIAN Registry experience

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Keywords: neuronopathic Gaucher disease, patient-led registry, patient-reported outcomes, observer-reported outcomes, burden of disease

Abstract

Background: Neuronopathic Gaucher disease (nGD) is a rare, progressive condition with substantial neurological and systemic burden and limited treatment options. Patient-reported outcome data are sparse and often rely on agnostic instruments that may not capture the full disease-specific impact. The Gaucher Registry for Development, Innovation and Analysis of Neuronopathic disease (GARDIAN) is a patient-led, multilingual, global registry designed to characterize disease burden over time and to evaluate nGD-specific patient- and caregiver-reported outcome measures.

27 Results: Between May 2022 and September 2025, 26 participants (10 patients
28 and 16 caregivers) contributed baseline data; 14 participants provided at least
29 one follow-up. Participants were recruited internationally. Most responses were
30 provided by caregivers of children, reflecting early disease onset. Twenty-five
31 patients had chronic nGD and one patient had acute nGD. At diagnosis,
32 commonly reported non-neurological manifestations included splenomegaly,
33 hepatomegaly, anaemia, abdominal distension, and thrombocytopenia, while
34 neurological features included abnormal eye movements, strabismus,
35 swallowing difficulties, ataxia, and laryngeal symptoms. At baseline, nearly all
36 patients were receiving enzyme replacement therapy, in conjunction with
37 supportive therapies such as calcium/vitamin D supplementation and
38 antiepileptic medications. Some patients reported additional therapies
39 including ambroxol, substrate reduction therapy, or gene therapy. Measures of
40 mental health and quality of life indicated mild-to-moderate depressive and
41 anxiety symptoms in a subset of respondents and moderate impairment in
42 paediatric quality of life. Disease-specific outcome scores suggested a mild-
43 to-moderate overall impact, with social-emotional domains more affected
44 than physical or self-care domains. Psychometric evaluation showed
45 acceptable internal consistency for both disease-specific instruments and
46 evidence of convergent validity with quality-of-life and disease-severity

anchors, although estimates were imprecise due to small sample size and attrition.

Conclusions: GARDIAN demonstrates the feasibility and value of a patient-led global registry for nGD and provides early evidence supporting disease-specific patient- and caregiver-reported outcome measurement. Larger studies are needed to strengthen validation, improve precision, and inform future clinical care and therapeutic development.

Keywords

Rare disease registry, neuronopathic Gaucher disease, patient-reported outcomes, burden of disease, quality of life.

Background

Gaucher disease (GD) is a rare inherited metabolic disorder due to variants in the *GBA1* leading to a deficiency of the lysosomal enzyme glucocerebrosidase. The deficiency results in the accumulation of the glycolipid glucocerebroside in lysosomes, and progressively in tissues and organs throughout the body (1). GD is classified into three distinct clinical subtypes, distinguished by the absence (type 1, GD1) or presence (type 2, GD2; and type 3, GD3) of central nervous system involvement. GD2 and GD3 are therefore categorised collectively as neuronopathic Gaucher disease (nGD) (1). Prevalence estimates for GD, encompassing all subtypes, range from 0.02 to 139.0 cases per 100,000

population. Among these, nGD , exhibit the lowest reported prevalence, typically between 0.02 and 0.08 cases per 100,000(2). GD2, typically presents in newborns and infants and is characterized by acute, rapidly progressing neurological deterioration that frequently leads to death in early infancy (3). GD3 represents the chronic neuronopathic form, marked by a gradual onset and slowly progressive neurological decline that extends throughout childhood and into adulthood (4, 5). nGD typically manifests before 2 years of age and is associated with a broad spectrum of neurological abnormalities, including muscle rigidity, ataxia, impaired voluntary movement, seizures, tremors, cognitive dysfunction, developmental delay, and visual disturbances. These manifestations are often challenging to manage and may be difficult to halt or reverse (1, 4-6).

As nGD progresses affected individuals often require increasing levels of support to perform activities of daily living (ADLs), e.g., eating, bathing, and ambulation (5). Beyond impairments in physical functioning, the disease is also associated with reductions in social engagement and participation in family or community activities. Emotional well-being may be adversely affected as well, with reports of diminished self-esteem and increased anxiety or depressive symptoms related to the awareness of disease-imposed limitations (5, 7).

Given these broad impacts, a central goal of nGD management is to improve quality of life by allowing them to perform their daily life activities. Most

88 approved therapies for Gaucher disease target the non-neurological
89 symptoms of GD1 (miglustat, eliglustat, taliglucerase alfa, velaglucerase alfa)
90 or GD1 and GD3 (imiglucerase). The investigational product venglustat has
91 recently shown efficacy in GD3 clinical trials and could be the first therapy
92 targeting the neurological effects of GD3 (8). Nevertheless, substantial unmet
93 needs remain for individuals with neuronopathic forms of the disease.

94 Advancing the understanding of the natural history of GD2 and GD3 is therefore
95 a critical priority to better characterise patient-specific symptoms and
96 challenges and to guide the development of effective, targeted therapeutic
97 approaches.

98 Rare disease registries play a critical role in addressing research gaps where
99 existing knowledge is limited or dispersed. These registries enable
100 characterisation of the natural history of disease and patterns of clinical
101 management, facilitate the identification and validation of patient-relevant
102 endpoints, support recruitment for clinical trials, and provide insight into real-
103 world treatment use and outcomes (9). The International Gaucher Alliance
104 (IGA), an international umbrella group representing national organisations for
105 patients with GD, established the Gaucher Registry for Development, Innovation
106 and Analysis of Neuronopathic disease (GARDIAN) to study patients with GD2
107 and GD3 worldwide in a systematic and standardised manner, and whose
108 development has been reported elsewhere (10). The International GARDIAN Ltd.

(IGL) is a not-for-profit body of the IGA, that operates the registry. The purpose of this patient-led registry is to raise awareness by serving as a research platform to provide evidence-based data for advancing disease management, designing safer treatments, and improving patient outcomes in nGD. The GARDIAN registry had three specific objectives: 1) To improve the understanding of the demographic, and disease-related characteristics of patients with nGD; 2) to further understand the extent of disease burden over time, including changes in symptoms and quality of life for patients, and 3) to assess the psychometric properties of disease-specific outcome measures for assessing quality of life over the natural course of nGD.

Methods

The GARDIAN registry is a multi-country longitudinal data collection initiative in which patients with nGD and/or their caregivers completed questionnaires at baseline and at six-month intervals for a maximum of thirty-six months.

Participants were recruited from communities by IGA member associations or bodies globally via social media, email, or any other available electronic platforms (<https://gardianregistry.org>).

Patient eligibility criteria included: 1) confirmed GD2 or GD3 diagnosis; 2) regular access to an internet-connected mobile device or computer, 3) a working email account; 4) provided an online informed consent to participate (adults),

or an online assent, if under legal age. Caregiver eligibility included: 1) aged 18 years or older who are the primary or co-primary caregiver of a patient with a confirmed GD2 or GD3 diagnosis; 2) legal authorized representative of the patient with a confirmed GD2 or GD3 diagnosis; 3) has regular access to an internet-connected mobile device, or computer and a working email account; and 4) who provided an online-informed consent to participate. Registration required the submission of diagnostic information which was then confirmed by medical staff nominated by the International GARDIAN Limited (IGL, wholly owned by the IGA).

Ethics and Data collection

The registry was approved by the Pearl Institutional Review Board (IRB) on 29 October 2021 and Cerner Enviza (now Oracle Life Sciences) IRB on 7 December 2021. The study was conducted according to the Declaration of Helsinki and with the ICH E6 (R1) Guideline for Good Clinical Practice E6(R2), and in compliance with national, international, and the European Data Protection Regulation 2016/679 (GDPR) on data protection and privacy. Data collection occurred from May 2022 to September 2025. All data collected were pseudonymised and non-attributable to a specific person. The IGA, Aparito and Cerner Enviza did not have access to the list of patients that were contacted through the local Patient Advocacy Groups (PAGs).

149 Questionnaires were accessible via the Atom5™ platform (Aparito) on
150 participants' devices and available in seven languages: English, French,
151 Spanish, German, Arabic, Japanese and Chinese.

152 At baseline, patient demographic, clinical characteristics and use of treatments
153 and healthcare resources were collected; caregivers also completed the
154 Paediatric Quality of Life Inventory (PedsQL) (11). At baseline and at six-month
155 intervals, participants were also asked to complete the following as applicable:
156 Patient Health Questionnaire 9 (PHQ-9) (12), Generalized Anxiety Disorder
157 Assessment 7 (GAD-7) (13), Patient Global Impression Scale – Severity (PGI-S),
158 PedsQL (11), and the nGD-PRO and nGD-ObsRO measures. PHQ9, GAD7 were
159 reported by patients only, while PedsQL and PGI-S were reported by both
160 patients and caregivers. Higher scores of PHQ-9, GAD-7 and PGI-S indicate
161 greater severity/disease burden, as opposed to PedsQL in which higher scores
162 reflect better quality of life.

163 nGD Patient-Reported Outcome (nGD-PRO) and Observer-Reported
164 Outcome (nGD-ObsRO) measures

165 The nGD-PRO scale measures nGD disease burden and is intended for children
166 with nGD aged 12 years or older and adults with nGD. The nGD-ObsRO is used
167 when patients with nGD, regardless of age, are incapable of completing a PRO
168 instrument independently. Details on the content validity of the nGD-PRO and
169 nGD-ObsRO are published elsewhere (10, 14). These disease-specific PRO

instruments include the following multi-item scales: symptoms, physical functioning, self-care, emotional well-being, daily and social activities, health-related concerns, travel limitations, overall health status, and impact on caregivers (14). In addition, the nGD-ObsRO measures caregiver impacts in four domains, i.e., stress from caring, level of fatigue, being anxious or panicky about the patient's health and being hopeful about the patient's health. The recall period for both nGD-PRO/ObsRO is 2 weeks. All the questions of the sub-scales, i.e., symptoms, physical functioning, self-care, social-emotional function and overall health, are scored on a numerical rating scale (0 to 10). Average scores are computed for each scale and an overall total score ranging 0-10, with lower scores indicating better quality of life. Additional questions, not included in the scales, are scored either on a numerical rating scale (0 to 10), either on a 4-point Likert scale or on a dichotomized score. To minimise participant burden, only items capturing the cardinal symptoms and key disease impacts relevant to individuals with nGD were included. Patients could choose to skip any questions they perceived as sensitive (e.g., those related to toileting incidents). Reminders were sent to the participants periodically; participants were given a time window of two months around assessment timepoints for completion. Participants also were asked to complete the nGD-PRO or nGD-ObsRO and the PGI-S, as applicable at two weeks follow-up for test-retest assessments. All

participants were followed from time of entry until the end of the registry, or until they decided to withdraw/were lost to follow up.

Data analysis

All the anonymized registry data were transferred to the registry database located at Cerner Enviza France SAS, who was responsible for data management and conducting both automatic and manual data checks.

Statistical analyses were conducted using R (version 4.2.2) and GraphPad Prism [(Version 10.6.1 (799))]. Continuous variables are summarised using descriptive statistics (n, mean, standard deviation, interquartile range, median, minimum, and maximum). Categorical variables are summarised showing the frequencies and percentages (n, %). Scores were computed for each of the outcome measures and reported for each assessment timepoint, as applicable. If any questionnaires for a given time point were missed, no data were imputed. If respondents skipped items, domain scores were calculated using available responses without imputation.

Due to the high attrition rate, sensitivity analysis to study changes or trends over time, using a linear mixed model (such as repeated measures ANOVA) was not possible.

Internal consistency reliability of the nGD-PRO and nGD-ObsRO was assessed using Cronbach's alpha coefficient, which was considered acceptable in the range of 0.70-0.95(15). Convergent validity was examined through Pearson's

correlations between nGD-PRO/ObsRO and PGI-S over the different time points, and through Spearman's correlation with PedsQL at baseline. Convergent validity criterion was met if a correlation coefficient >0.50 was found (16). Test-retest reliability was assessed using the Intraclass Correlation Coefficient (ICC) in participants with complete baseline and retest data who remained stable at retest relative to baseline, based on the PGI-S. Significance was set at a two-tailed p -value of <0.05 .

Results

Demographics and clinical profile of respondents

Data from a total of 26 participants (10 patients; 16 caregivers) were analysed (Table 1). Participants resided in Egypt (8), the United Kingdom (6), the United States of America (4), Sweden (3), and the following countries with 1 participant each: Serbia, Haiti, China, Lithuania, and Pakistan. Data were provided by patients ($n=10$, 38.5%) and parents/caregivers ($n=16$, 61.5%) with equal proportions of female and male participants. All but one were diagnosed with GD3. One infant, 1 year of age at registry entry, was diagnosed with GD2. Nearly all patients lived with their parents/siblings, and one resided with a partner/spouse. Overall, a third had at least one family member diagnosed with nGD, and a third had a family member diagnosed with Parkinson's Disease (Table 1).

[Table 1 placeholder]

Fourteen participants (5 patients/9 caregivers) completed at least one follow-up report at some time point after baseline. In total, nineteen and twenty-one follow-up reports were submitted by patients and caregivers, respectively.

Signs and symptoms at diagnosis and evolution over time

Among all respondents, the number of signs and symptoms present at diagnosis were 9.35 (2-26) (mean, range). The most frequently reported symptoms at diagnosis clustered into two broad categories. Non-neurological manifestations including splenomegaly (n=21, 81%), hepatomegaly (n=18, 69%), anaemia (n=17, 65%), abdominal distension (n=15, 58%) and thrombocytopenia (n=14, 54%). Neurological features included abnormal eye movement (n=10, 38%), strabismus (n=8, 31%), swallowing difficulties (n=7, 27%), ataxia (n=6, 23%) and laryngeal symptoms (n=6, 23%), which the latter encompassing laryngeal spasm, choking or apnoea. In addition, 20% of patients (n=5) with GD3 exhibited behavioural difficulties at diagnosis. The single patient with GD2 presented with a broader constellation of symptoms, including fatigue, laboured breathing, poor feeding, recurrent fevers and infections, impaired linear growth and weight gain, hypertonia, and both speech and hearing deficits.

Figure 1 illustrates the percent change of patients with a given symptom between diagnosis and registry entry. In general, non-neurological symptoms were more commonly present at diagnosis, except for Gaucher-related lung disease, bone pain, fatigue and gaucheroma, while the frequency of

253 neurological symptoms generally increased between diagnosis and registry
254 entry.

255 Use of treatments, medical devices and healthcare services

256 At baseline, 96% (n=25) of patients were on enzyme replacement therapy (ERT).
257 Additional treatments included calcium supplement/vitamin D (n=15, 58%),
258 antiepileptic medications (n=9, 35%), ambroxol (n=7, 27%), anti-depressants
259 (n=3, 12%), bisphosphonates (n=3, 12%) and other nutritional supplements (n=3,
260 12%). Spasticity management medications were reported by 8% (n=2) of
261 patients. One patient reported the use of substrate reduction therapy, and one
262 patient reported receiving gene therapy.

263 Fourteen (54%) participants reported no surgical intervention at baseline. The
264 reported surgery procedures included those related to nGD (n=7, 27%),
265 tracheostomy (n=3, 12%), percutaneous endoscopic gastrostomy (PEG) (n=3,
266 12%), partial splenectomy (n=2, 8%). One patient underwent total splenectomy
267 and one underwent spinal surgery.

268 Medical device use was limited with 15 (58%) patients reporting not using any of
269 the options displayed. Among those reporting use of assistive devices patients
270 used glasses (n=8, 31%), feet orthosis (n=4, 15%), wheelchair (n=4, 15%), back
271 brace (n=3, 12%), hearing aids (n=3, 12%), and aids for personal hygiene such as

272 walk-in shower (n=2, 8%) or bath lifts (n=1, 4%). One patient (4%) reported using
273 a ramp at home.

274 The frequency of use of healthcare services showed the following breakdown:
275 case manager services (n=10, 38%), adapted school/teaching (n=6, 23%), home
276 care (n=6, 23%), mental health services (n=4, 15%), help line support (n=3, 12%),
277 institutional long-term care (n=3, 12%) and personal assistant for self-care
278 (n=3, 12%).

279 Patient- and observer-reported outcomes

280 Figure 2 reports mean scores for the PHQ-9, GAD-7, PedsQL, and PGI-S. PHQ9,
281 which measures depressive symptoms, had a mean (SD) score of 11.0 (7.15)
282 across eight participants. At follow-up, mean (SD) PHQ-9 scores were 13.0 (3.0)
283 at six months and 9.0 (5.6) at twelve months, respectively. All observed scores
284 fell within the range typically interpreted as indicative of mild to moderate
285 depressive symptoms (PHQ-9 score range: 0-27)(17). At baseline, severity of
286 anxiety, using the GAD-7, had mean (SD) scores of 11.5 (8.41) across six
287 participants, 11.3(4.04) at six months and 6.0 (4.24) at twelve months, reflecting
288 mild to moderate anxiety in this small group (GAD-7 score range: 0-21)(18).
289 At baseline, the mean (SD) score for the self-reported PedsQL was 52.8 (24.25)
290 and was 65.1 (12.17) for the observer-reported PedsQL; these scores indicate
291 moderate impairment in quality of life. There were no substantial differences
292 across the PedsQL domains between patients and caregivers. Caregivers

293 tended to report fewer perceived challenges compared to patients, particularly
294 in school functioning.

295 According to the PGI-S, patients experienced mild fluctuations in perceived
296 symptom severity, but there was no clear and sustained trend toward
297 improvement or worsening over the observation period.

298 [Figure 2 placeholder]

299 For the nGD-PRO, mean (SD) total score at baseline was 3.3(2.80) (score range
300 0-10), indicating a little-to-moderate impact of GD on health-related quality of
301 life. The nGD-PRO mean score tended to increase over time. Higher nGD impact
302 is seen on the social-emotional domain, rather than the physical or self-care
303 domains (Figure 3).

304 [Figure 3 placeholder]

305 Regarding nGD-Obs RO, the mean (SD) value at baseline was 3.2 (2.01). Over
306 time, caregivers showed a slightly more positive perception of health-related
307 quality of life domains than patients (Figure 4). Interestingly, the social-
308 emotional scale scores were lower in younger patients, as reported by their
309 caregivers, than those self-reported by patients, indicating a worse impact of
310 nGD as patients grow older.

311 [Figure 4 placeholder]

Attendance to school/work and impact of nGD

Both the nGD-PRO and nGD-ObsRO evaluated other aspects of the impact of nGD on patients' daily activities (Figure 5). At baseline, most patients attended school or were engaged in part-time or full-time work. In the 14 days preceding baseline, most patients reported not missing any school or work (n= 5, 35%), while others missed few or even 4 or more days (n=9, 65%) over the last 14 days. Approximately one-third of patients (n=4, 33.%) reported no difficulty or stress in keeping up with school or work responsibilities, whereas 25% (n=3) reported having difficulty or stress "sometimes," and 17% (n=2) reported such challenges "half of the time." Overall, most respondents indicated that their school, school district, or workplace supportive towards their health needs.

[Figure 5 placeholder]

Support services

Figure 6 displays the distribution of responses regarding support services reported by patients (left column) and carers (right column). Support for emotional and physical health, as reported by both patients and carers, is limited; however, carers reported greater support at home and at school/work for the patients they care for. Connectedness to peers was done mostly through in-person support groups (baseline, higher sample size), and with a mix of online support and loose involvement as time progressed. Patients perceived

healthcare provider (HCP) support more positively than caregivers. At baseline, most patients considered that HCPs were very supportive, whereas caregivers rated HCPs mainly as moderately supportive.

[Figure 6 placeholder]

Caregiver impacts

The overall mean score of caregiver impacts was 5.6 (2.13) (n=14) at baseline, while by domain they were 4.8 (3.81), 4.4 (2.82) and 6.0(3.95) for stress, fatigue and anxiety levels, respectively, suggesting a moderate impact of nGD on caregivers (Figure 7). In contrast, caregivers felt moderately to very hopeful about the patients' future health with a mean score of 7.2 (2.42) (Figure 7).

[Figure 7 placeholder]

Psychometric properties of nGD-PRO/ObsRO

Internal consistency

Both nGD-PRO and nGD-ObsRO show good internal consistency reliability and exceed the prespecified alpha of ≥ 0.7 (Table 2). However, uncertainty is high as shown by the wide confidence interval (CI) values and the small sample size in both groups.

Table 2. Psychometric properties: internal consistency, test-retest reliability and construct validity

Test	nGD-PRO	nGD-ObsRO
Cronbach's alpha [CI]	0.955 [0.538, 0.984] n=7	0.754 [0.485, 0.875] n=14
Intra-class correlation (ICC) [CI]	0.909 [-0.893, 0.998] p-value=0.0648	0.987 [0.813, 0.999] p-value=0.00132*

	n=3	n=4
PedsQL		
Spearman r	-0.9009	-0.5667 [0.410, 0.855]
p-value	p=0.0095**	p=0.1206
Number of pairs	n=7	n=9
PGI-S		
Pearson r	0.5680 [-0.1544, 0.8946]	0.6081 [0.1391, 0.8542]
p-value	p=0.1106	p=0.0162*
Number of pairs	n=9	n=15

Construct validity

Construct validity of both nGD-PRO and nGD-ObsRO was assessed by examining their correlations with established clinical outcome measures of quality of life and disease severity, specifically the PedsQL (self- and observer-reported versions) and the PGI-S. The criterion for convergent validity was met, as all correlation coefficients exceeded the pre-specified threshold of $r > 0.5$.

Test/retest reliability

Test-retest reliability was measured among participants who remained stable at the time of retest compared to baseline PGI-S, and who had complete baseline and the retest time point of two weeks. For nGD-PRO, the ICC showed high dispersion and uncertainty due to the very small sample. For nGD-ObsRO, the ICC shows promise as precision was higher, but still should be confirmed in a larger sample of participants (Table 2). Good reliability was shown for all domains in both measures, except for the patient-reported social/emotional domain, which was below the good reliability threshold (Figure 8).

[Figure 8 placeholder]

Discussion

The results of the GARDIAN Registry have contributed to the knowledge of patient characteristics, the natural history and burden of nGD, revealing a wide range of impacts of nGD on patients and caregivers. GARDIAN results demonstrated how nGD affects patients across several dimensions of quality of life over time and showed that the impact might be different between young and adult patients, particularly in the social and emotional domain. The impact of nGD on caregivers on stress, anxiety and fatigue levels was also captured with the nGD-ObsRO. These findings highlight the importance of evaluating the patients' and caregivers' experience with specific instruments.

GARDIAN is the first patient-led initiative to establish a registry for nGD, available in seven languages, and designed to reach a global community. Its goal is to support comprehensive data collection for the GD2 and GD3 subtypes, for which limited or no targeted therapies currently exist. Historically, the major internal GD registries have been industry-sponsored, including the International Collaborative Gaucher Group (ICGG) Registry, launched in 1991 by Genzyme (now Sanofi), and the Gaucher Outcome Survey initiated in 2010 by Shire (now Takeda), each aligned with the approval of imiglucerase and velaglucerase, respectively (19, 20). Additional national GD registries such as the French (21), the

388 Spanish (22) and the UK registry (23) are led by academic or clinical
389 institutions. Within this landscape, GARDIAN was developed to address
390 persistent knowledge gaps for individuals with neuronopathic GD, particularly
391 the need for patient-centered perspectives. A distinctive feature of GARDIAN, is
392 the inclusion and validation of two neuronopathic-specific clinical outcome
393 assessments (COA) as part of the core objectives (10).

394 Profile of respondents align with current knowledge of Gaucher disease?
395 The respondent profile observed in GARDIAN is broadly consistent with what is
396 known about nGD. The proportion of parent or caregiver respondents (62%),
397 primarily caring for children under 18 years, exceeded that of patient
398 respondents (38%), all of whom were adults. Among the 26 patients included,
399 25 had GD3, which aligns with the higher prevalence, later onset, and longer life
400 expectancy associated with GD3 compared with GD2. The very low global
401 prevalence of GD2, coupled with limited participation, resulted in
402 underrepresentation of GD2 in the cohort. The single patient with GD2 was a 1-
403 year old at registry entry and the symptoms reported were consistent with
404 those described in the literature(6) although further details are needed to
405 determine the exact clinical phenotype (24). As expected, this patient
406 presented with a more severe phenotype compared with patients with GD3(3).
407 The mean age at diagnosis for GD3 patients was 1.5 years, while the GD2 patient

408 was diagnosed before one year of age consistent with previous reports (25)
409 and with the consensus definitions distinguishing GD2 and GD3 (3).

410 Twenty-seven percent of patients reported family history of Gaucher disease
411 and 35% of Parkinson's disease, also consistent with the literature (7). However,
412 information about GBA mutations in GD patients' relatives was not collected.

413 The type of both non-neurological and neurological signs and symptoms at
414 diagnosis are in agreement with those previously described in early childhood
415 GD2/GD3 patients (5, 25, 26). Behavioural issues (including, continuous crying,
416 excessive anger, physically/verbally aggressive, explosive temper, impatience,
417 making excessive demands, social withdrawal, recurring behaviour) were also
418 present at diagnosis in 20% of GD3 patients, and increased to 42% at registry
419 entry. Anger and aggression have been reported to be more prevalent in male
420 GD3 patients, and in both males and females a lower cognitive ability,
421 representing a major impact on patients' and caregivers' quality of life (27).

422 The frequency of symptoms reported reflect the evolution of the neuronopathic
423 disease, with an increase of neurological symptoms from diagnosis until the
424 time of registry entry (3). In contrast, non-neurological symptoms decreased,
425 particularly haematological symptoms, such as bleeding, low haemoglobin
426 levels and low platelet count, as well as swollen abdomen, and spleen and liver
427 enlargement, most likely in response to treatment as 25 out of 26 patients were

428 receiving ERT at baseline (28–33), while neurological symptoms increased as
429 not specifically targeted by ERT. In addition to ERT, two patients reported having
430 a partial splenectomy, and one had a full splenectomy at baseline. One patient
431 reported treatment with substrate reduction therapy, although it is not a
432 licensed indication for GD2/GD3 types.

433 Overall, the cohort profile was consistent with the epidemiology of nGD, with
434 most participants having chronic neuronopathic disease and caregiver
435 respondents predominating due to early onset and paediatric impact.

436 Patient-reported outcomes and burden of disease

437 Beyond clinical manifestations, the registry highlights substantial functional
438 and psychosocial burden, including impacts on activities of daily living,
439 participation in school and work, and emotional well-being.

440 Although no statistical comparisons were made due to the low number of
441 responses, nGD-ObsRO scores (n=14) over time were generally lower than
442 those reported by patients in the nGD-PRO (n=7), particularly in the
443 social/emotional domain and overall health, showing a difference in how the
444 patient's own health status is perceived. In this case, the PRO was completed by
445 adult patients, while caregivers were caring for younger populations, which
446 may also explain the difference. These results underscored the importance of
447 developing both PRO and ObsRO measures.

448 The burden of disease on patients was found to be mild to moderate for
449 depression and anxiety, assessed by PHQ-9 and GAD-7, and moderate
450 impairments in health-related quality of life as assessed by PedsQL. Symptom
451 severity was also rated mild to moderate.

452 nGD-ObsRO is the first questionnaire that specifically measures the impact of
453 nGD on caregivers in four domains: stress, fatigue, anxiety and feeling of hope.
454 Scores were in the moderate range for stress, fatigue and anxiety, while
455 caregivers felt moderate to very hopeful for the patient's future health. The
456 existing literature on measuring the impacts on caregivers of GD patients is
457 rather limited. Caregiver burden in GD had been previously measured in Japan
458 using instruments targeted to caregivers of patients with rare lysosomal
459 storage disorders and heart failure (34). These instruments showed that
460 caregiver burden was moderately increasing over time in GD3 and decreasing
461 in GD2 (although initial burden was higher than GD3). Another report from
462 China described moderate-to-severe depression and anxiety in caregivers of
463 GD patients (not specified) using generic measures (e.g., SF-36), and
464 anxiety/depression PROs (35). Incorporating this domain into the nGD-ObsRO
465 allows to have a more comprehensive perspective of nGD caregivers'
466 experience.

467 Psychometric properties of nGD-PRO/ObsRO

468 The registry also generated early evidence supporting the measurement

469 performance of the nGD-specific instruments, including internal consistency

470 and convergent validity against established anchors.

471 Health outcomes of GD patients had been previously assessed with generic

472 forms such as the SF-36 Health Survey, EuroQoL-5 Dimension (EQ-5D) or

473 PedsQL, among others (7), and with a GD1-specific PRO (36), which was recently

474 updated to include a part targeting GD2/GD3 patients as well (37). However,

475 there were no specific PRO and observer-reported outcome measures to

476 capture the impact of neuronopathic GD2/GD3, which led to development of

477 the nGD-PRO and nGD-ObsRO measures by the IGA through a multi-

478 stakeholder co-creation process (10, 14). Building on previous qualitative

479 interviews undertaken by the IGA and Cerner Enviza to establish the content

480 validity of nGD-PRO/ObsRO measures in GD2 and GD3 (unpublished), the

481 current study, nested within the registry, represents a further step towards the

482 provision of a robust self-report measure of HRQOL in GD2 and GD3 patients.

483 Cronbach's alpha coefficients for nGD-PRO and nGD-ObsRO were 0.955 (95%CI:

484 0.538-0.984; n=7) and 0.734 (95%CI: 0.410-0.855; n=15). While alpha values

485 between 0.7 and 0.9 indicate strong consistency, the extremely high value of the

486 nGD-PRO alpha may indicate some redundancy, that will need to be further

487 investigated. In addition, the minimum sample size required in the pre-specified
488 analysis to obtain an alpha of 0.7 with a precision of ± 0.2 , and a significance
489 level of 0.05, was 25 patients and 25 caregivers, which in this case was not
490 attained. Internal consistency results, though promising, need to be confirmed
491 in further larger studies to minimize variability and increase accuracy.

492 Test-retest reliability ICC of nGD-PRO was high, i.e., 0.909 (CI: -0.893 to 0.998,
493 $p=0.0648$, $n=3$), though not significant due to higher dispersion. Only three
494 patients had complete pairs of observations (baseline and retest), were
495 available, and results will have to be confirmed with larger observations. ICC for
496 nGD-ObsRO was 0.987 (CI: 0.813–0.999, $p=0.00132$, $n=4$), but the number of pairs
497 was also very low. The fact that out of 26 participants, only eight completed
498 both the baseline and retest, and from this only seven had stable PGI-S values,
499 reduced eligible data for analysis.

500 Construct validity assessment revealed statistically significant correlation
501 between nGD-PRO and PedsQL ($r=-0.9009$, $p<0.01$), indicating that the nGD-PRO
502 could be valuable to measure the quality of life of nGD patients. However, the
503 correlation nGD-ObsRO and the observer-reported versions of PedsQL was not
504 significant due to high variability.

505 One potential explanation is that whereas most of the self-reported versions
506 were the young adult questionnaire (just one patient responded to the child

questionnaire), responses from four different observer-reported PedsQL versions (infant, toddler, teen and young adult) were included. These versions cover slightly different concepts of interest particularly in the social/emotional and cognitive domains across different age groups.

In summary, validation results should be interpreted with caution and further validation in a larger sample sought.

Limitations

GARDIAN evidenced the difficulty of recruiting and retaining participants in the registry over long periods, which resulted in a decreasing sample size over the 36 months and prevented drawing conclusions from the analysis. Participant engagement and retention long-term are among the main challenges when it comes to such registries.

A unique feature of GARDIAN was its worldwide reach and decentralised approach, facilitated by the translation of the registry platform into seven languages, and the flexibility of reporting either by patients themselves or their caregivers. The platform was co-designed with IGA advocates ensuring comprehensive data collection, quality of the data and ease of use. While decentralisation provides advantages to vulnerable populations versus in-clinic attendance, it is not completely burden-free, particularly during the screening phase. The eligibility questionnaire was long, and participants had to upload documentation to confirm their diagnosis etc. Once included,

528 participants had to respond to the baseline questionnaire to provide
529 demographics data, clinical symptoms at diagnosis and registry entry, and
530 respond to six PRO/ObsRO. The long-term nature of longitudinal registries, has
531 been also associated with higher attrition(38). Reminders were sent during
532 follow-up time points every six months, but the response rate over time
533 suggests that additional nudges, follow-up calls in between, to receive
534 feedback on the entered data, financial incentives or gamification options
535 could have helped to sustain engagement. A combination of different
536 motivational approaches is recommended to maximise engagement, but these
537 should be ideally underpinned by a theoretical framework (39), which in the
538 case of GARDIAN would have been very difficult to implement due to the broad
539 cultural and geographical diversity that the registry was targeting.

540 Lessons learned

541 The implementation of GARDIAN provided important insights into the
542 opportunities and challenges of establishing a global, patient-led,
543 decentralised registry in an ultra-rare disease population.

544 *Awareness of the existence of the registry and its purpose.*

545 Evaluation of findings demonstrated that awareness of the registry did not
546 consistently translate into enrolment. In a focus group conducted to explore low
547 participation, 75% of participants had heard of the registry, yet only one of
548 twelve was actively enrolled. Stakeholder feedback, from users, Aparito, Oracle

549 and the IGL Board of Directors and staff team similarly identified recruitment as
550 a major hurdle. These findings highlight that awareness campaigns alone are
551 insufficient without ensuring that possible recruits had clarity of the registry
552 purpose, data governance, and tangible (albeit long term) participant benefit.
553 Interest increased when registry processes and intended impact were clearly
554 explained, suggesting that structured onboarding and clear and effective
555 communication are essential in rare disease contexts.

556 *Burden of Participation/Sustained Engagement*

557 Participation was experienced as burdensome. Participants reported limited
558 personal time, the feeling that they had to repeat the same information across
559 forms, emotional fatigue when describing symptoms, and uncertainty about
560 how their data would be used.

561 Attrition over 36 months limited longitudinal analyses. Automated reminders
562 alone were insufficient to sustain participation. Evaluation findings suggest that
563 ongoing engagement strategies—including feedback loops, community
564 updates, and peer support—are critical to retain engagement. Sustainability
565 planning, including long-term funding and human support staffing for
566 engagement, must therefore be embedded from inception of any such study.

567 *Shortcomings in Functionality*

568 In addition, as questionnaires were designed for completion within a single
569 session (this approach simplified data handling and reduced partial datasets),

570 this did not accommodate the unpredictable and personally pressurised
571 schedules of caregivers managing the complex care of the participant. The
572 absence of a “save-and-return” function may have resulted in increased
573 discontinuation during longer assessments. This experience highlights the
574 importance of flexible, interruption-tolerant digital design with auto-save
575 features and modular data entry in rare disease registries for populations with
576 high-burden disease.

577 *Structure Inhibited Third Party Support*

578 A number of clinicians were enthusiastic about the registry but due to lack of
579 funds and requirements of anonymity of data were unable to support
580 participants in adding data to the registry. Additionally, notwithstanding
581 attempts to assist participants resource constraints combined with the need for
582 anonymity of the data subject limited the ability to provide personalised
583 engagement support.

584 *Absence of Availability of the Registry on “smart” devices*

585 Technical and design limitations, particularly on mobile devices, were identified
586 as barriers. User experience and mobile optimisation were also proved to be a
587 barrier to easy engagement. Given that many participants rely on smartphones
588 for day-to-day activities, a simplified mobile-first design, allowing for cross-
589 device testing, and intuitive navigation will be essential for renewed and
590 sustained engagement.

591 *Need for Participant Access to their own data*

592 Although the registry was designed to collect data from patients and
593 caregivers, participants expressed a strong desire for reciprocal value
594 (feedback) from participation. They wished to be able to access and track their
595 own longitudinal data, to use the registry as a personal health record, and to be
596 able to share outputs with clinicians. It is perceived that these expectations
597 reflect a broader shift toward participatory data ownership models.
598 Incorporating participant dashboards or exportable summaries are believed
599 likely to improve retention and perceived value.

600 *Local Challenges to Access*

601 Although GARDIAN was available in seven languages, language inclusion alone
602 did not ensure consistent global access. Significant patient cohorts reside in
603 countries where none of these languages are widely used, effectively limiting
604 participation. Furthermore, after implementing a Chinese-language version,
605 regulatory and governance complexities limited recruitment through Chinese
606 patient organisations and clinicians. These experiences demonstrate that
607 linguistic translation must be accompanied by early assessment of jurisdiction-
608 specific regulatory, digital, and partnership environments.
609 Additionally, in some parts of the world easy access to a computer and/or
610 computer literacy was not assured. In some locations, data input would have
611 been more successful if support for the process was available.

Conclusions

GARDIAN was unique as it was patient-driven, i.e., patients and families were involved in its design, ensured the outcomes were relevant to the nGD community, and owned the registry. The data collected belongs to the IGL and will be used solely for the benefit of the patient community. The registry was online and aimed to be fully decentralised from clinical sites. Similar initiatives have been reported in other rare diseases, albeit with a much shorter duration and limited to just one geographic region (40) or with extensive healthcare professional involvement (40, 41). It has also highlighted the significant challenges around the sustainability of online rare disease registry initiatives with an ambitious global outreach.

The insights collected by GARDIAN contributes to the limited body of knowledge of disease specific, patient-relevant outcomes from neuronopathic GD2 and GD3 types. Further validation of the nGD-specific PRO and ObsRO psychometric properties in a larger sample is warranted but this primarily data set gives great foundation for its applicability as outcome measures in future clinical trials and clinical care.

A patient lead and patient owned registry can be of tremendous value in both highlighting the unmet need of an ultra-orphan condition and seeking to stimulate further investigation into potential therapies. The results of the registry and learnings highlighted above allow us to refine the structure and design of

633 registry to assure greater recruitment more sustained participant engagement

634 whilst still focussing on the patients' experience of nGD.

635

Tables

Table 1. Demographic characteristics of GARDIAN participants

Variable	Value	Self-reported	Caregiver-reported
Total Participants	n=26	n=10	n=16(62%)
Gender			
Female	13 (50%)	4	9
Male	13 (50%)	6	7
Type of respondent			
Patient	10 (38%)		
Parent/caregiver ^s	16 (62%)		
Type of Gaucher disease			
GD2	1 (4%)	--	1
GD3	25 (96%)	10	15
Age of patient at registry entry* (median, range)	12.0, 1-28		
<12 years	10 (40%)	--	10
12 to <18 years	5 (20%)	1	4
18 to <30 years	10 (40%)	8	2
Age of patient at diagnosis (median, range)	1.0, 0-26		
<12 years	25 (96%)	9	16
12 to <18 years	--	--	--
18 to <30 years	1 (4%)	1	--
Ethnicity**			
White	9 (43%)	2	7
Mediterranean/Arab	3 (14%)	--	3
Mediterranean	2 (10%)	--	2
Middle Eastern	1 (5%)	--	1
Asian	4 (19%)	2	2
Black/African	1 (5%)	--	1
American/Caribbean			
Mixed	1 (5%)	1	--
Family history			
Gaucher disease	8 (30%)		
Siblings	4 (50%)	3	1
Cousin	2 (25%)	--	2
Siblings and cousin	2 (25%)	--	2
Parkinson's disease	9 (35%)		
Parents	1 (11%)	--	1
Grandparents	4 (44%)	2	2
Uncles/aunts	1 (11%)	--	1
Great grandparents	1 (11%)	--	1
Great uncles/aunts	1 (11%)	--	1
Parents and grandparents	1 (11%)	1	--
Living situation			

With parents/siblings	25 (96%)	9	16
With partner/spouse	1 (4%)	1	--
Highest Level of Education***			
Early childhood education	5 (22%)	1	4
Primary education/Elementary school	3 (13%)	--	3
Secondary education (Junior-Senior)	10 (44%)	6	4
Bachelor's or equivalent/College graduate	1 (4%)	1	--
Master's or equivalent/Post-graduate	2 (9%)	2	--
Never went to school	2 (9%)	--	2
Employment			
Still in full time education	12 (46%)	3	9
Not yet enrolled in school	4 (15%)	--	4
Employed – part time	3 (11%)	3	--
Employed – full time	1 (4%)	--	1
Self-employed	2 (8%)	2	--
Unemployed – looking for work	2 (8%)	1	1
On long-term disability (>6 weeks) and Unemployed – not looking for work	1 (4%)	1	--
Prefer not to answer/don't know	1 (4%)	1	--

§One parent reported three affected children

*Results based on 25 patients due to missing data for one patient

**Results based on 21 patients (due to local regulations, the question on ethnicity was not asked in all countries).

***Results based on 23 patients due to missing data for 3 patients

Figure titles and legends

Figure 1. Change in non-neurological and neurological signs and symptoms between diagnosis and registry entry.

Figure 2. The extent of burden of disease over time. Higher PHQ-9, GAD-7 and PGI-S scores indicate worsening of symptoms. Higher PedsQL scores indicate better quality of life. Number of observations appears on top of the error bars.

Figure 3. Mean total and domain nGD-PRO scores at baseline and each follow-up time point. Number of observations on top of error bars.

Figure 4. Mean total and domain nGD-ObsRO scores at baseline and each follow-up time point. Number of observations on top of error bars.

Figure 5. Impact of nGD on school/work and support received. Percentages of responses at baseline from patients (nGD-PRO) and caregivers (nGD-ObsRO) were considered together.

Figure 6. Percentage of responses at baseline and follow-up time points from patients (left column) and caregivers (right column) regarding seeking emotional (a, b) and physical (c, d) support, peer connectedness (e, f), and perceived HCP support (g, h).

Figure 7. The extent of impact on caregivers at baseline and each follow-up timepoint as reported in the nGD-ObsRO.

Figure 8. ICC per nGD-PRO/ObsRO dimensions and total score. Good reliability is considered if $ICC > 0.75$

References

1. Stirnemann J, Belmatoug N, Camou F, Serratrice C, Froissart R, Caillaud C, et al. A Review of Gaucher Disease Pathophysiology, Clinical Presentation and Treatments. *Int J Mol Sci.* 2017;18(2).
2. Castillon G, Chang SC, Moride Y. Global Incidence and Prevalence of Gaucher Disease: A Targeted Literature Review. *J Clin Med.* 2022;12(1).
3. Schiffmann R, Seigny J, Rolfs A, Davies EH, Goker-Alpan O, Abdelwahab M, et al. The definition of neuronopathic Gaucher disease. *J Inherit Metab Dis.* 2020;43(5):1056–9.
4. Tylki-Szymanska A, Vellodi A, El-Beshlawy A, Cole JA, Kolodny E. Neuronopathic Gaucher disease: demographic and clinical features of 131 patients enrolled in the International Collaborative Gaucher Group Neurological Outcomes Subregistry. *J Inherit Metab Dis.* 2010;33(4):339–46.
5. Schiffmann R, Turnbull J, Krupnick R, Pulikottil-Jacob R, Gwaltney C, Hamed A, et al. Gaucher disease type 3 from infancy through adulthood: a conceptual model of signs, symptoms, and impacts associated with ataxia and cognitive impairment. *Orphanet J Rare Dis.* 2025;20(1):171.
6. Roshan Lal T, Seehra GK, Steward AM, Poffenberger CN, Ryan E, Tayebi N, et al. The natural history of type 2 Gaucher disease in the 21st century. *Neurology.* 2020;95(15).
7. Feng J, Gao Z, Shi Z, Wang Y, Li S. Patient-reported outcomes in Gaucher's disease: a systematic review. *Orphanet J Rare Dis.* 2023;18(1):244.
8. Sanofi's venglustat met all primary endpoints in a phase 3 study of type 3 Gaucher disease [press release]. Paris, 2/2/2026 2026.
9. Hageman IC, van Rooij IALM, de Blaauw I, Trajanovska M, King SK. A systematic overview of rare disease patient registries: challenges in design, quality management, and maintenance. *Orphanet Journal of Rare Diseases.* 2023;18(1).
10. Collin-Histed T, Stoodley M, Beusterien K, Elstein D, Jaffe DH, Revel-Vilk S, et al. A global neuronopathic gaucher disease registry (GARDIAN): a patient-led initiative. *Orphanet J Rare Dis.* 2023;18(1):195.
11. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care.* 2001;39(8):800–12.
12. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA.* 1999;282(18):1737–44.
13. Johnson SU, Ulvenes PG, Oktedalen T, Hoffart A. Psychometric Properties of the General Anxiety Disorder 7-Item (GAD-7) Scale in a Heterogeneous Psychiatric Sample. *Front Psychol.* 2019;10:1713.
14. Beusterien K, Isaacs, J., Jaffe, D., Elstein, D., Stoodley, M., Davies, E.H., Collin-Histed, T. PCR148 Patient involvement in the development of outcomes

- measures specific to neuronopathic Gaucher disease type 2 and type 3 to assess HRQOL over the disease journey. *Value in Health*. 2022;25(12):S419.
15. Tavakol M, Dennick R. Making sense of Cronbach's alpha. *Int J Med Educ*. 2011;2:53–5.
 16. Abma IL, Rovers M, van der Wees PJ. Appraising convergent validity of patient-reported outcome measures in systematic reviews: constructing hypotheses and interpreting outcomes. *BMC Res Notes*. 2016;9:226.
 17. Kroenke K, Spitzer RL, Williams JB. The PHQ–9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606–13.
 18. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD–7. *Arch Intern Med*. 2006;166(10):1092–7.
 19. Weinreb NJ, Vom Dahl S, Cappellini M.D. Long term data from the ICGG Gaucher Registry: Clinical parameters after 10 years of treatment with imiglucerase. *Blood*. 2009;114(22):3590.
 20. Weinreb NJ. The international cooperative Gaucher group (ICCG) Gaucher registry. *Best Pract Res Clin Haematol*. 2023;36(4):101522.
 21. Stirnemann J, Vigan M, Hamroun D, Heraoui D, Rossi-Semerano L, Berger MG, et al. The French Gaucher's disease registry: clinical characteristics, complications and treatment of 562 patients. *Orphanet J Rare Dis*. 2012;7:77.
 22. Giraldo P, Pocovi M, Perez-Calvo J, Rubio-Felix D, Giralto M. Report of the Spanish Gaucher's disease registry: clinical and genetic characteristics. *Haematologica*. 2000;85(8):792–9.
 23. Zimran A, Belmatoug N, Bembi B, Deegan P, Elstein D, Fernandez-Sasso D, et al. Demographics and patient characteristics of 1209 patients with Gaucher disease: Descriptive analysis from the Gaucher Outcome Survey (GOS). *Am J Hematol*. 2018;93(2):205–12.
 24. Donald A, Brothwell S, Cabello BM, Ehrstedt C, Fernandez-Fructuoso JR, Fernandez-Marin E, et al. 250 cases of "type 2 Gaucher disease": A novel system of clinical categorisation and evidence of genotype: Phenotype correlation. *Mol Genet Metab*. 2025;145(2):109124.
 25. Schwartz IVD, Goker-Alpan O, Kishnani PS, Zimran A, Renault L, Panahloo Z, et al. Characteristics of 26 patients with type 3 Gaucher disease: A descriptive analysis from the Gaucher Outcome Survey. *Mol Genet Metab Rep*. 2018;14:73–9.
 26. Donald A, Jones SA, Hughes DA, Church HJ, Consortium G, Cox TM. Gaucher disease type 3: Classification of the chronic neuronopathic variant informed by genotype in a phenotypically diverse cohort. *Genet Med*. 2025;27(9):101502.
 27. Abdelwahab M, Potegal M, Shapiro EG, Nestrail I. Previously unrecognized behavioral phenotype in Gaucher disease type 3. *Neurol Genet*. 2017;3(3):e158.

28. Lee NC, Chien YH, Wong SL, Sheen JM, Tsai FJ, Peng SF, et al. Outcome of early-treated type III Gaucher disease patients. *Blood Cells Mol Dis*. 2014;53(3):105–9.
29. Sechi A, Deroma L, Dardis A, Ciana G, Bertin N, Concolino D, et al. Long term effects of enzyme replacement therapy in an Italian cohort of type 3 Gaucher patients. *Mol Genet Metab*. 2014;113(3):213–8.
30. El-Beshlawy A, Tytki-Szymanska A, Vellodi A, Belmatoug N, Grabowski GA, Kolodny EH, et al. Long-term hematological, visceral, and growth outcomes in children with Gaucher disease type 3 treated with imiglucerase in the International Collaborative Gaucher Group Gaucher Registry. *Mol Genet Metab*. 2017;120(1–2):47–56.
31. Gumus E, Karhan AN, Hizarcioglu-Gulsen H, Demir H, Ozen H, Saltik Temizel IN, et al. Clinical-genetic characteristics and treatment outcomes of Turkish children with Gaucher disease type 1 and type 3: A sixteen year single-center experience. *Eur J Med Genet*. 2021;64(11):104339.
32. Stanescu S, Correcher Medina P, Del Castillo FJ, Alonso Luengo O, Arto Millan LM, Belanger Quintana A, et al. Clinical Outcomes of Patients with Chronic Neuropathic Form of Gaucher Disease in the Spanish Real-World Setting: A Retrospective Study. *Biomedicines*. 2023;11(10).
33. Goker-Alpan O, Ivanova MM, Pathak R, Wright E. Enzyme replacement therapy in infants and very young children with Gaucher disease using velaglucerase alfa: a single-center experience. *Front Pediatr*. 2025;13:1613599.
34. Koto Y, Narita A, Noto S, Okada M, Ono M, Baba T, et al. Burden of caregivers of patients with neuronopathic and non-neuronopathic Gaucher disease in Japan: A survey-based study. *Mol Genet Metab Rep*. 2023;36:100994.
35. Xu J, Bao H, Qi X, Wang J, Yin H, Shang C, et al. Family caregivers of rare disease: A survey on health-related quality of life in family caregivers for Gaucher disease patients in China. *Mol Genet Genomic Med*. 2021;9(9):e1760.
36. Elstein D, Belmatoug N, Deegan P, Goker-Alpan O, Hughes DA, Schwartz IVD, et al. Development and validation of Gaucher disease type 1 (GD1)-specific patient-reported outcome measures (PROMs) for clinical monitoring and for clinical trials. *Orphanet J Rare Dis*. 2022;17(1):9.
37. Narita A, Koto Y, Noto S, Okada M, Ono M, Baba T, et al. Development and evaluation of a patient-reported outcome measure specific for Gaucher disease with or without neurological symptoms in Japan. *Orphanet J Rare Dis*. 2024;19(1):11.
38. Doumen M, De Cock D, Van Lierde C, Bettrains A, Pazmino S, Bertrand D, et al. Engagement and attrition with eHealth tools for remote monitoring in chronic arthritis: a systematic review and meta-analysis. *RMD Open*. 2022;8(2).

39. Lu T, Lin Q, Yu B, Hu J. A systematic review of strategies in digital technologies for motivating adherence to chronic illness self-care. *npj Health Systems*. 2025;2(1):13.
40. Gaggiano C, Del Bianco A, Sota J, Gentileschi S, Ruscitti P, Giacomelli R, et al. A patient-driven registry on Behcet's disease: the AIDA for patients pilot project. *Front Med (Lausanne)*. 2023;10:1188021.
41. Nakshbandi G, Moor CC, Antoniou K, Cottin V, Hoffmann-Vold AM, Koemans EA, et al. Study protocol of an international patient-led registry in patients with pulmonary fibrosis using online home monitoring: I-FILE. *BMC Pulm Med*. 2023;23(1):51.

Declarations

Ethics approval and consent to participate

The registry was approved by the Pearl Institutional Review Board (IRB) on 29 October 2021 and Cerner Enviza (now Oracle Life Sciences) IRB on 7 December 2021. Participants provided informed consent through the online platform.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

EFM, SK, CF and EHD are employees of Aparito, a wholly owned subsidiary of Eli Lilly and Company

Joseph Milce, SR, MF and KB were fulltime employees of Cerner Enviza (Oracle Life Sciences) during the time GaRDIAN was conceptualized and implemented.

SRV received travel, research grants, and honoraria from Sanofi-Genzyme, Takeda, and Pfizer. In addition, she has served on advisory boards for Takeda and Spur. The Gaucher Unit receives support from Sanofi to participate in the International Collaborative Gaucher Group (ICGG) Gaucher Registry and from Takeda for the Gaucher Outcome Survey (GOS).

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Author's contributions

EFM drafted the manuscript, analysed PRO data and performed construct validity analysis and contributed to the interpretation of the data.

SK contributed to GARDIAN data collection and data management and analysed all demographics and health-related questionnaire data, as well as the analysis on internal consistency and test-retest reliability.

CF contributed to GARDIAN data collection and data management, and registry implementation and maintenance.

KC and SRV provided scientific advice, guidance on registry development and substantively revised the manuscript.

Jeremy Manuel contributed to GARDIAN leadership and oversight, and substantively revised the manuscript

Joseph Milce, SR, MF and KB contributed to the conception and design of the GARDIAN registry, oversight of the implementation team and ongoing collaboration with life science companies focused on nGD.

EHD contributed to the conception and design of the GARDIAN registry, data collection and substantively revised the manuscript.

TCH contributed to the conception and design of the GARDIAN registry and substantively revised the manuscript.

All authors read and approved the final manuscript.

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Figures

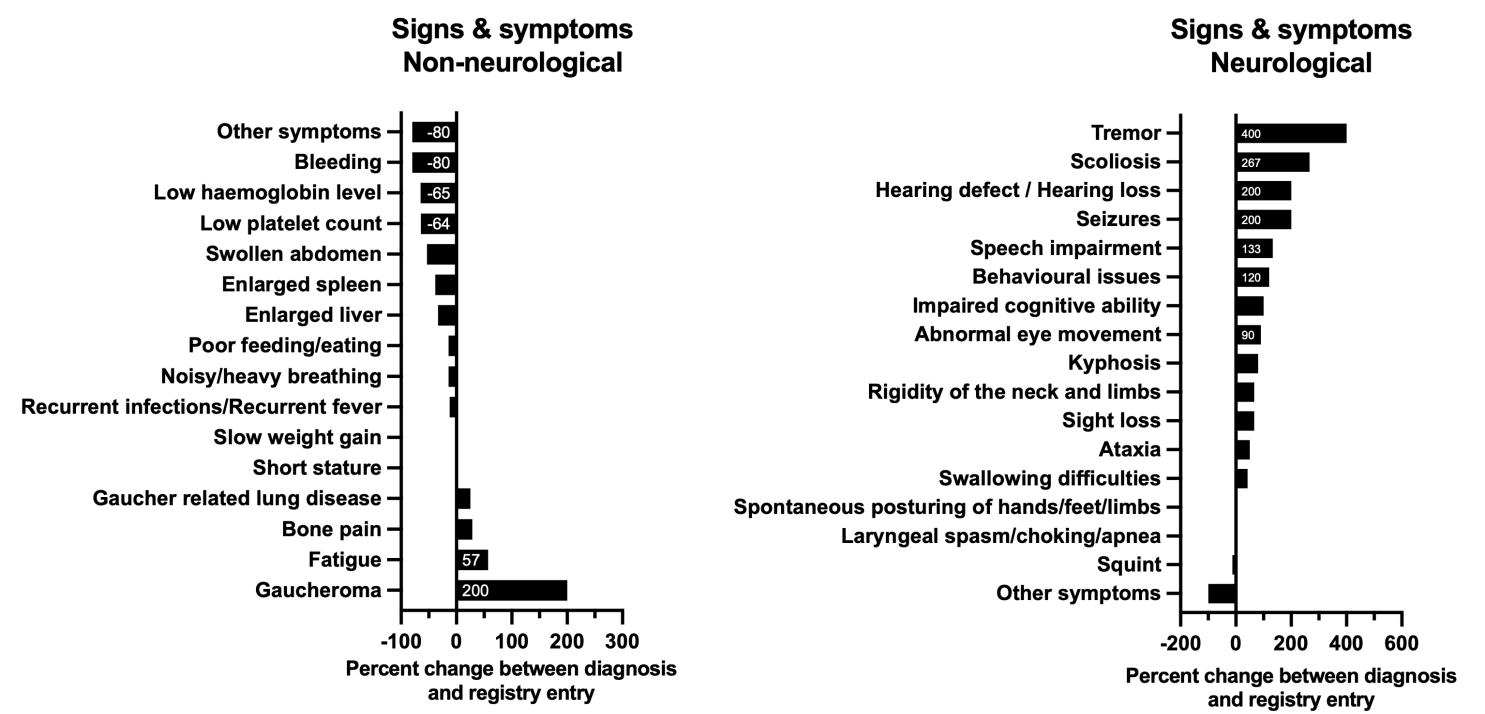


Figure 1

Change in non-neurological and neurological signs and symptoms between diagnosis and registry entry.

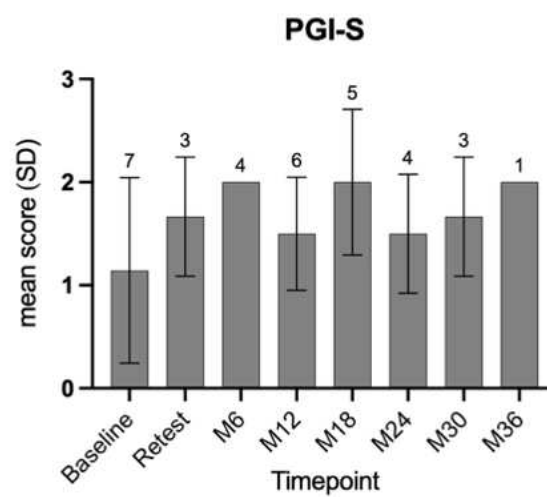
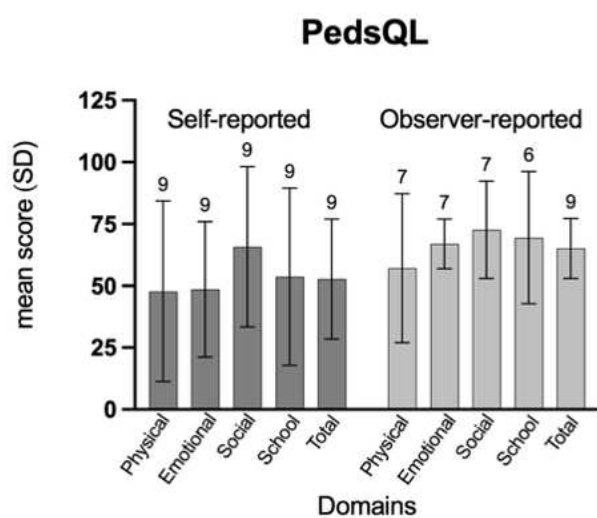
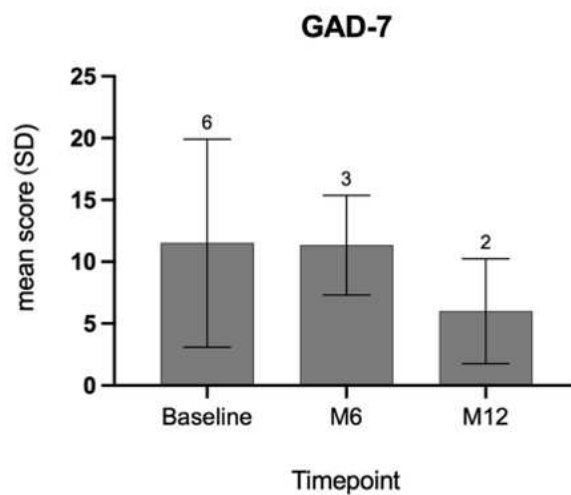
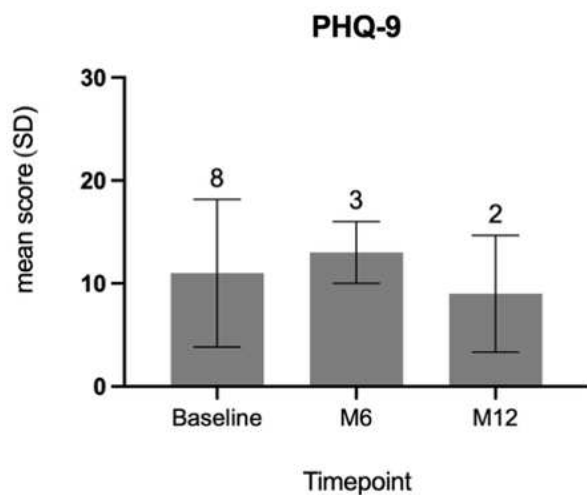


Figure 2

The extent of burden of disease over time. Higher PHQ-9, GAD-7 and PGI-S scores indicate worsening of symptoms. Higher PedsQL scores indicate better quality of life. Number of observations appears on top of the error bars.

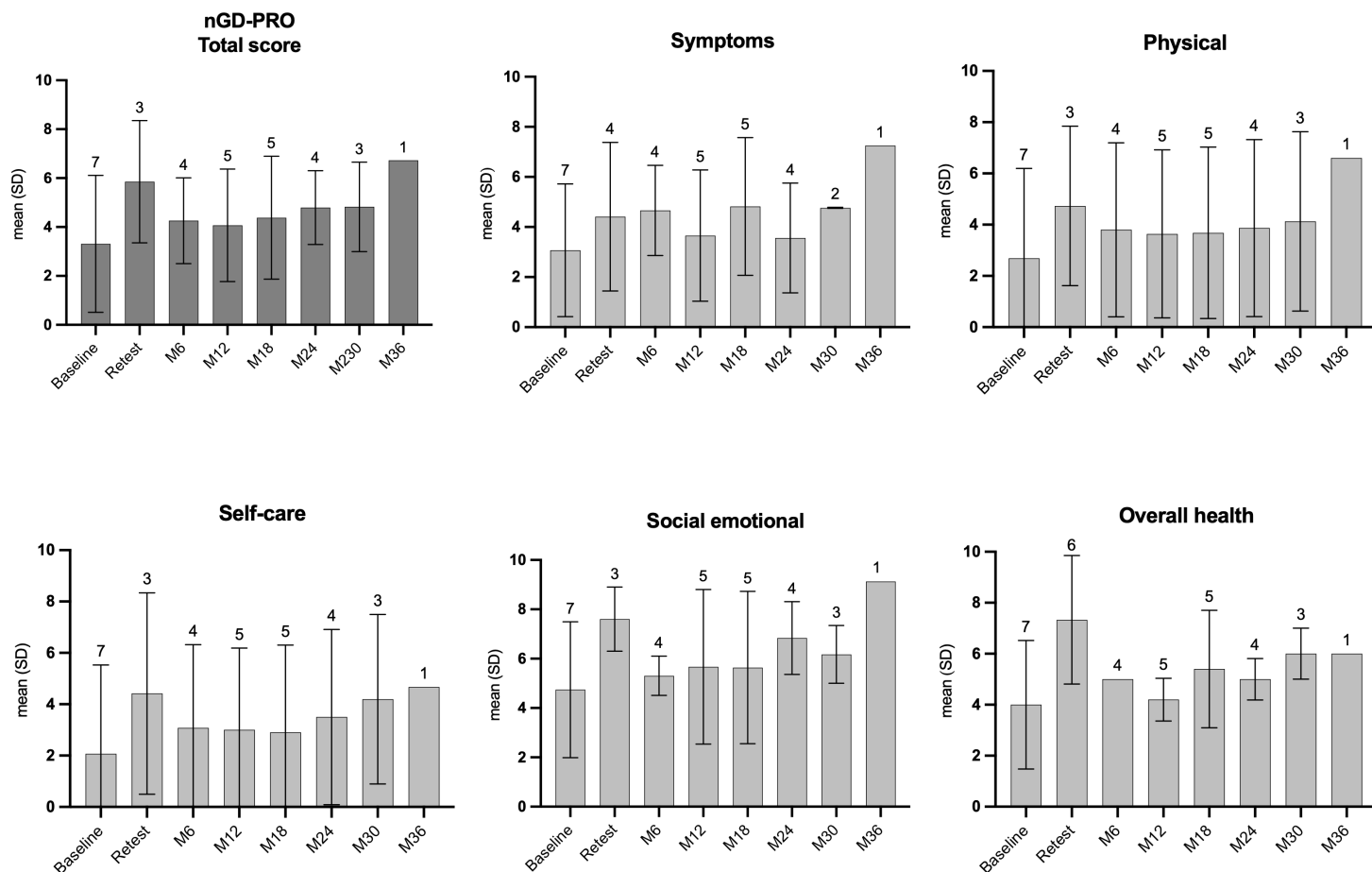


Figure 3

Mean total and domain nGD-PRO scores at baseline and each follow-up time point. Number of observations on top of error bars.

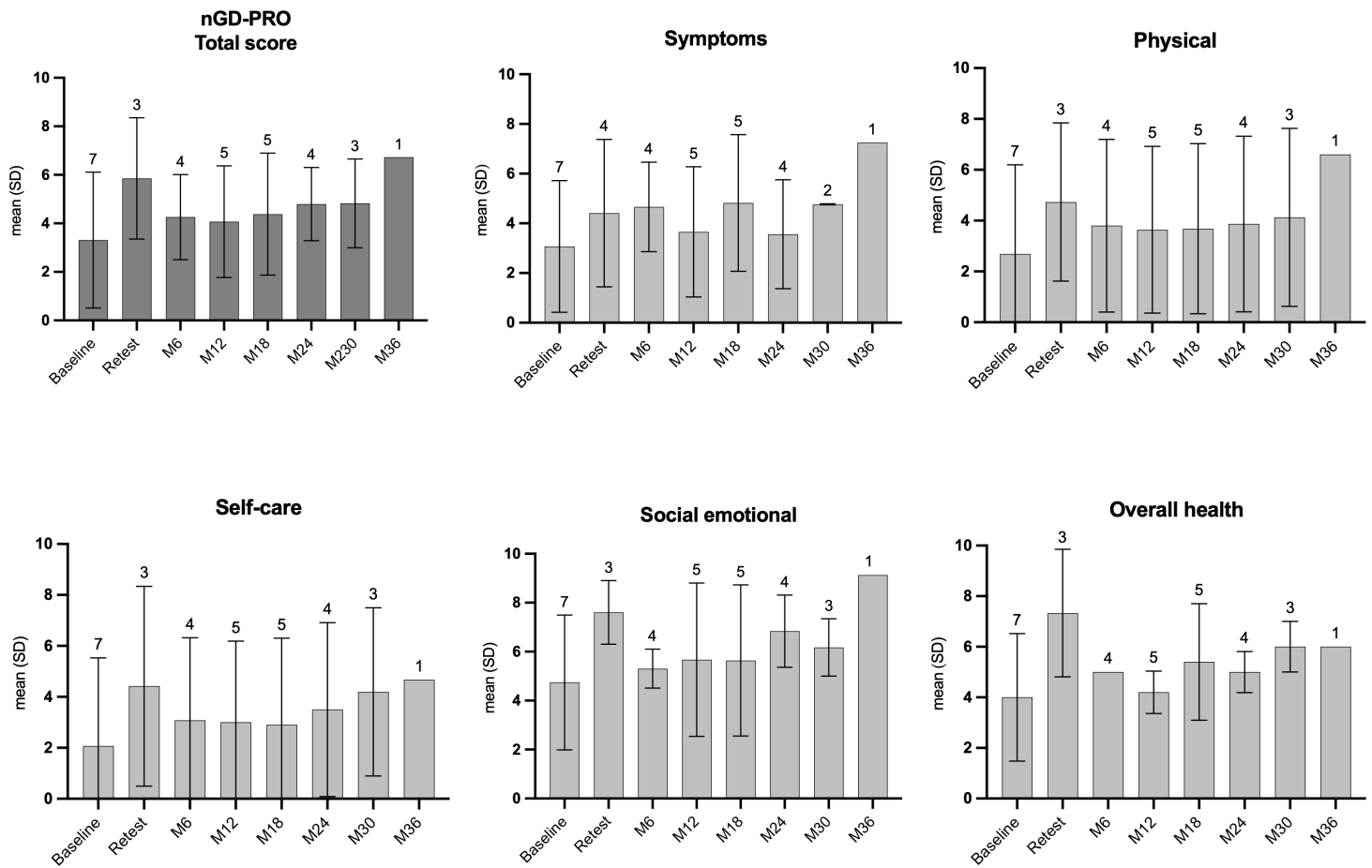


Figure 4

Mean total and domain nGD-ObsRO scores at baseline and each follow-up time point. Number of observations on top of error bars.

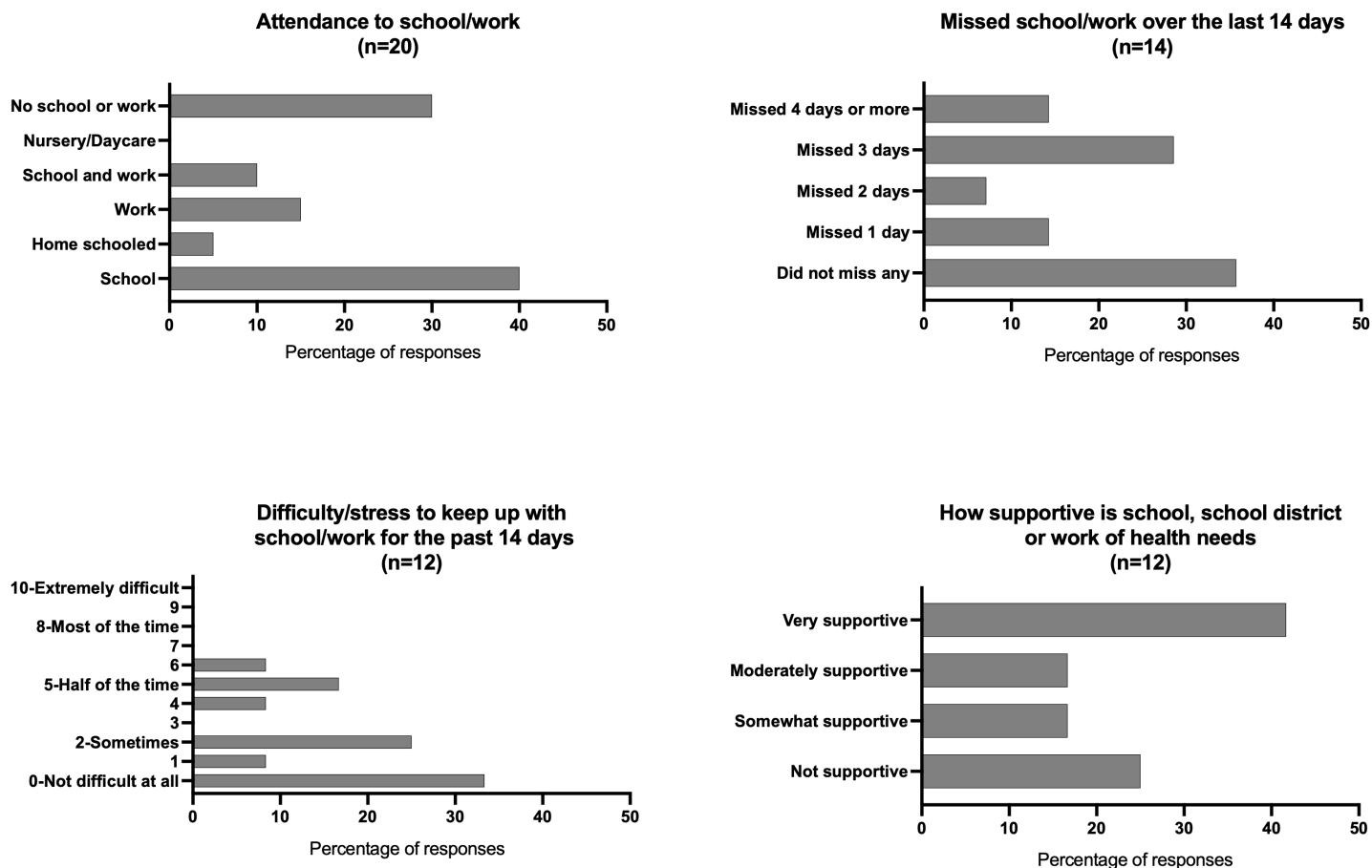


Figure 5

Impact of nGD on school/work and support received. Percentages of responses at baseline from patients (nGD-PRO) and caregivers (nGDObsRO) were considered together.

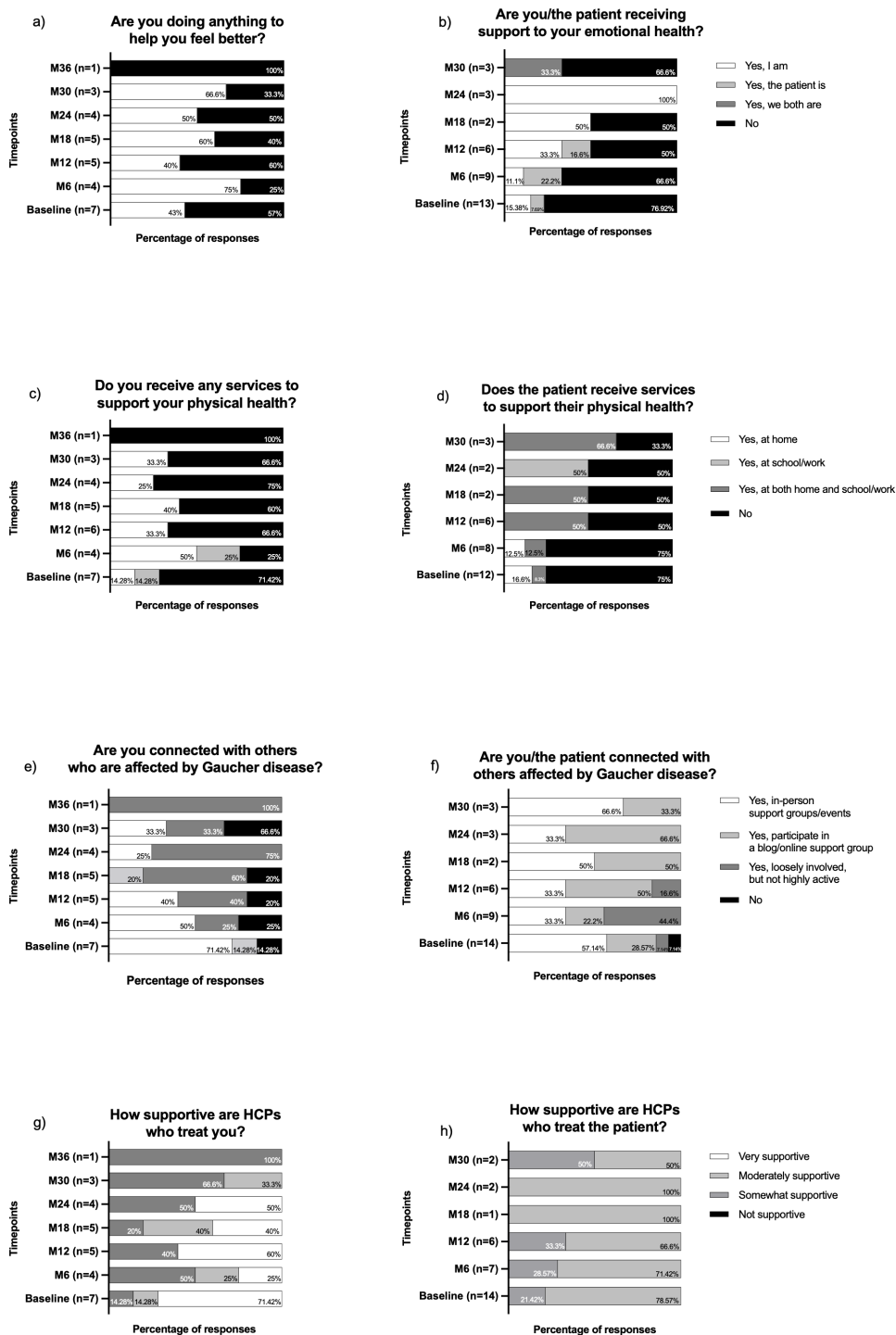


Figure 6

Percentage of responses at baseline and follow-up time points from patients (left column) and caregivers (right column) regarding seeking emotional (a, b) and physical (c, d) support, peer connectedness (e, f), and perceived HCP support (g, h).

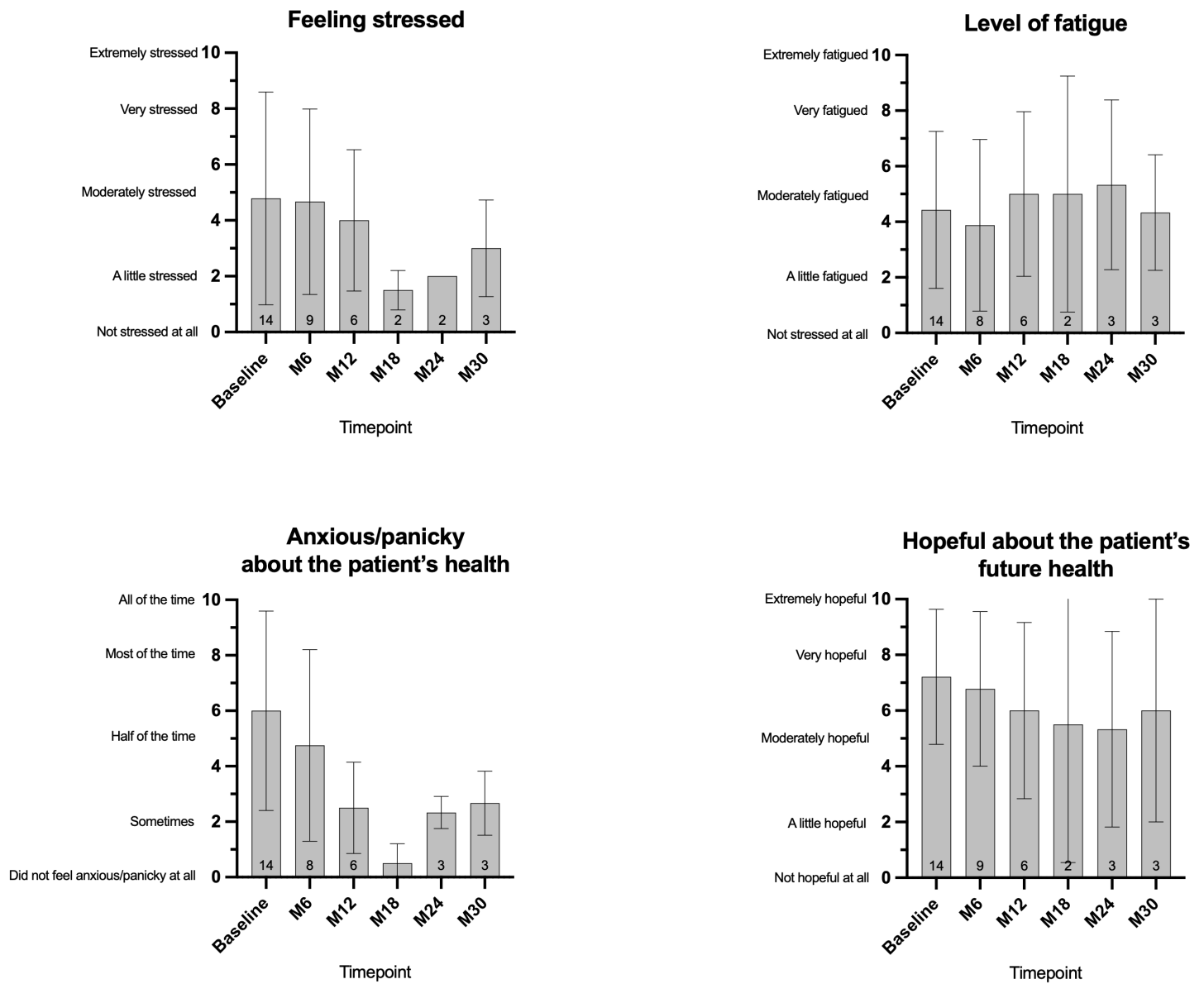


Figure 7

The extent of impact on caregivers at baseline and each follow-up timepoint as reported in the nGD-ObsRO.

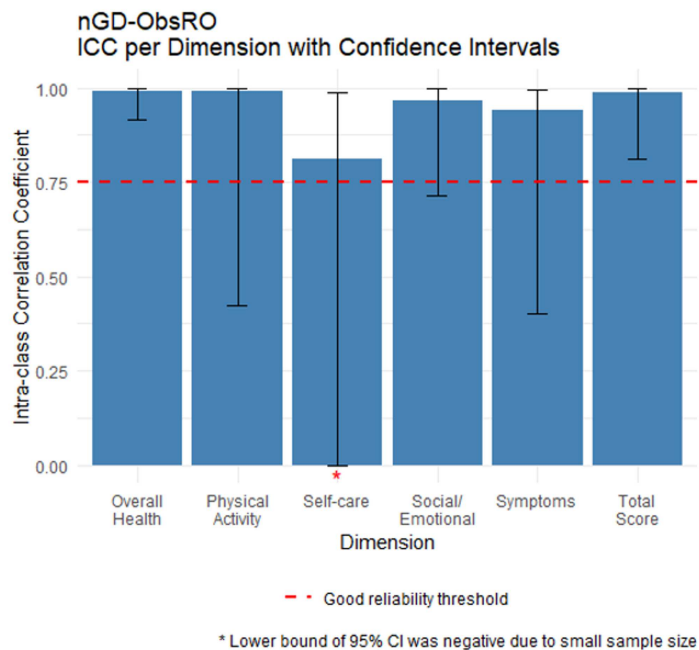
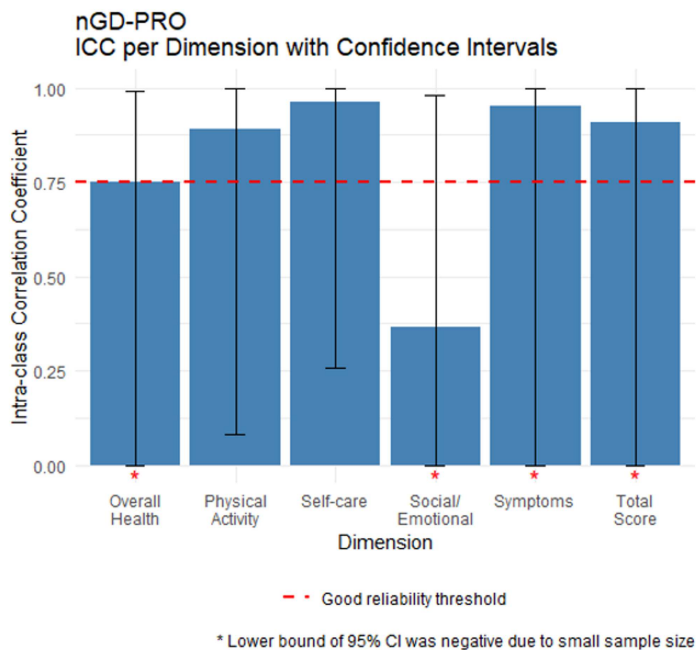


Figure 8

ICC per nGD-PRO/ObsRO dimensions and total score. Good reliability is considered if $ICC > 0.75$