



# Burden Among Caregivers of Pediatric Patients with Neurofibromatosis Type 1 (NF1) and Plexiform Neurofibroma (PN) in the United States: A Cross-Sectional Study

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## ABSTRACT

**Introduction:** Patients with neurofibromatosis type 1 (NF1) may develop plexiform neurofibromas (PNs) that can cause disfigurement, pain, and dysfunction, and may even be life-threatening. Studies have indicated NF1-PN can substantially impact the quality of life (QoL) of pediatric patients. However, research on caregiver burden is scarce.

**Methods:** Caregivers of pediatric patients ages 2–18 years with NF1-PN in the USA were recruited through the Children’s Tumor Foundation to participate in an online cross-sectional survey (December 2020–January 2021). Caregiver burden was measured using the Zarit Burden Interview (ZBI), and productivity loss from patient care was measured using the Work Productivity and Activity Impairment questionnaire, adapted for caregiving (WPAI:CG).

**Results:** Ninety-five caregivers were recruited with a median age of 44.0 years. Most were female (88.4%), white/Caucasian (85.3%), and did not have NF1 or PN (86.3% and 89.5%, respectively). Commonly reported health conditions among caregivers include anxiety (48.4%) and depression (34.7%). On the ZBI (range 0–88; higher = greater burden), mean (SD) scores were 23.0 (13.8) and 12.7% of caregivers reported moderate–severe (scores 41–60) or severe burden (scores 61–88). Fifty-six caregivers were employed and working in the 7 days prior to completing the WPAI:CG. They reported missing an average of 6.9% of their working hours and an average reduction of 17.3% of on-the-job effectiveness, contributing to 22.3% loss in work productivity. Among all 95 caregivers, an average of 17.2% of regular daily activities were impaired.

**Conclusions:** The burden among caregivers of pediatric patients with NF1-PN is considerable and underscores an unmet need for better disease management.

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**Keywords:** Neurofibromatosis type 1; Plexiform neurofibromas; Caregiver burden; Work productivity loss; Activity impairment; Cross-sectional study; Zarit Burden Interview; WPAI; Quality of life

### Key Summary Points

This real-world study characterized the burden of caring for pediatric patients in the USA who had neurofibromatosis type 1 with plexiform neurofibromas (NF1-PN), a condition with multiple comorbidities that require specialized healthcare.

Caregivers were considerably burdened as a result of providing care for their pediatric patient with NF1-PN, experiencing one-fifth of overall loss in their ability to fully attend work as required along with diminished effectiveness while working (i.e., taken together, overall loss in work productivity) and impairment in activities of daily living.

Our findings highlight that both the patient with NF1-PN and their caregiver experience a substantial burden from the disease, underscoring an unmet need for better management of NF1-PN.

## INTRODUCTION

Neurofibromatosis type 1 (NF1) is a genetic disease occurring in approximately 1 in 3000 live births [1] that is characterized by cutaneous abnormalities such as café au lait skin spots and iris Lisch nodules, and tumors within the peripheral and/or central nervous system [2, 3]. These physical manifestations are often accompanied by neurocognitive disabilities such as attention-deficit/hyperactivity disorder (ADHD; experienced by approximately 50% of pediatric patients) [4]. Plexiform neurofibromas (PNs) are benign peripheral nerve tumors occurring in up to 50% of patients with NF1 [5, 6] that are associated with significant pain and disability, disfigurement, organ compression, motor impairments, visual dysfunction, and may even be life-threatening [2, 7–10]. As a

result, pediatric patients with NF1-PN incur a heavy clinical burden of disease and severely diminished quality of life (QoL) [11–14].

Caregivers may also face considerable challenges when caring for pediatric patients with NF1-PN. The multifaceted concept of caregiver burden can be used to refer to the physical, psychological/emotional, social, and financial problems experienced when caring for a chronically ill patient [15–17]. Furthermore, a distinction is sometimes made between the objective burden, defined as observable disruptions or changes to the caregivers' life and household (e.g., financial costs, time lost from work, etc.), and the subjective burden, defined as the caregiver's emotional and psychological response to these changes/disruptions (e.g., stress, anxiety) [15, 16, 18]. Studies may therefore assess the overall caregiver burden or choose to focus on specific domains/aspects of this burden.

Overall caregiver burden has been assessed among parents of children across a wide range of chronic conditions, including chronic pain, status epilepticus, cerebral palsy, cystic fibrosis, and spina bifida, among others [19–21]. In these cross-sectional studies, parents reported a substantial overall burden across multiple domains including physical, psychological, economic, and social ones [19, 21]. In particular, parents of pediatric patients with chronic conditions reported considerable lost productivity at work and during regular activities outside of work, as well as high financial costs in providing healthcare for their child [20, 22–24]. Furthermore, caring for a chronically ill child takes a substantial emotional and psychological toll, as evidenced by high rates of self-reported anxiety and depression among caregivers [24–26].

To date, real-world studies describing the burden experienced by caregivers of pediatric patients with NF1-PN are limited. However, one recent survey study by Wiener et al. [27] found that approximately one-third of parents reported feeling alone in caring for their child with NF1. Caregivers of children with NF1 who perceived themselves to be a lone parent were in turn more likely to be classified as having clinically significant levels of distress [27].

Caregiver burden has been shown to increase with indicators of greater medical complexity and poorer overall health status among pediatric patients [19, 22]. The burden of caring for pediatric patients with NF1-PN, who have multiple comorbidities and require specialized healthcare, may be significant and could negatively impact QoL. Therefore, a better understanding of the burden experienced by this caregiver population is warranted. To address this knowledge gap, the present real-world study aimed to evaluate the self-reported burden of care and work productivity and activity impairment among caregivers of pediatric patients with NF1-PN in the USA.

## METHODS

### Study Design and Sample Selection

In this cross-sectional study, caregivers of pediatric patients aged 2–18 years with NF1-PN were recruited to participate in an online survey administered between December 1, 2020 and January 14, 2021. These one-time surveys were used to evaluate caregivers' demographic and clinical characteristics, overall burden, and work productivity and activity impairment. Caregivers were recruited from the NF Registry, an NF patient-centered database managed by the Children's Tumor Foundation, an international non-profit organization aimed at expanding knowledge of NF and advancing care for patients. To participate in the study, caregivers were required to meet the study inclusion criteria based on self-report. Eligible caregivers had to be at least 18 years of age at the time of survey participation, a primary caregiver of a pediatric patient with NF1-PN who was treatment naïve or had been treated with selumetinib, a resident of the USA, and able to read, write, and understand English. There were no exclusion criteria in the present study.

A subset of the pediatric patients of these caregivers were included in a separate observational, cross-sectional study by the present authors which investigated the clinical and humanistic burden among pediatric patients with NF1-PN in the USA [28]. Pediatric patients

described in the study were between the ages of 2 and 18 years, treatment naïve or newly treated with selumetinib (defined as at most 1 month of treatment), and residents of the USA. Those between the ages of 8 and 18 years participated in the survey component of the study and additionally were required to be able to read and write in English to be eligible for participation. Pediatric patients who were previously treated with selumetinib but were no longer receiving active treatment, treated with off-label medications for NF1-PN (i.e., received treatment with binimetinib, cobimetinib, mirdametinib, or trametinib), or pregnant were excluded from the study. Pediatric patients treated with off-label medications for NF1-PN and those treated with selumetinib for more than 1 month were excluded because the study was designed to measure the burden of the disease, rather than the effectiveness of treatment.

### Sample Measures and Outcomes

Study measures included caregiver-reported demographic and clinical characteristics, while study outcomes included caregiver-reported burden and work productivity and activity impairment assessed using self-reported survey instruments.

#### *Caregiver Burden*

Caregiver burden was assessed using the Zarit Burden Interview (ZBI), a 22-item self-reported survey instrument designed to measure the caregiver's perceived level of burden as a result of caring for a patient [29]. Initially developed to measure the burden associated with the care of community-dwelling older persons [30], the ZBI has since been administered to caregivers of youth and young adults with chronic conditions across multiple studies [19, 21, 25, 26, 31]. The ZBI questions comprise five domains: (1) burden in the relationship (six items), (2) emotional well-being (seven items), (3) social and family life (four items), (4) finances (one item), and (5) loss of control over one's life (four items). Responses include a five-point Likert scale ranging from "never" (0) to "nearly always" (4). Overall scores total the summed

responses from each item (range 0–88), with higher scores indicating a greater perceived burden related to caregiving for their child. Specifically, total scores are interpreted as follows: 0–21 = little or no burden, 21–40 = mild to moderate burden, 41–60 = moderate to severe burden, and 61–88 = severe burden.

### ***Work Productivity and Activity Impairment***

To measure lost productivity due to caring for a pediatric patient with NF1-PN, the Work Productivity and Activity Impairment Questionnaire, adapted for caregiving (WPAI:CG), was administered [32]. This six-item, self-reported survey instrument was designed to capture reductions in work productivity and then adapted to assess the impact of a patient's disease on their caregiver's level of productivity [33]. Although the WPAI:CG was initially adapted in caregivers for chronically ill older adults, it has since been used in caregivers of pediatric patients with chronic conditions [24, 32]. In the WPAI:CG, overall lost productivity comprises the amount of time missed from work due to caregiving (i.e., absenteeism) and the amount of reduced productivity while at work (i.e., presenteeism). Responses are measured as numerical values (i.e., number of hours) for some questions and on a scale from "no effect" (0) to "completely prevented" (10) for others. Absenteeism is calculated as the work hours missed due to caregiving divided by the sum of the hours missed and the hours worked. Presenteeism is calculated as the degree to which caregiving affected productivity while working (measured on a scale from 0 to 10, with 0 indicating "no effect" and 10 indicating that caregiving "completely prevented me from working") divided by 10. Work productivity loss is defined as overall work impairment, i.e., absenteeism plus presenteeism. It is calculated as  $\text{absenteeism} + [(1 - \text{absenteeism}) \times \text{presenteeism}]$ . Absenteeism, presenteeism, and overall work productivity loss were expressed as percentage productivity losses, with higher values indicating a greater proportion of time lost from work (i.e., less productivity). Regular activity productivity loss was defined as the extent to which caregiving affected productivity while engaging in regular daily activities.

### **Ethics Approval and Participant Consent Statements**

This retrospective survey study was conducted in accordance with the ethical standards of the Declaration of Helsinki. The study was approved by the WCG IRB (reference number 20202853). All participants signed an informed consent form regarding the publication of the data they contributed to this study.

### **Statistical Analyses**

Descriptive summary measures were calculated for all outcomes of interest for the caregiver sample. Continuous variables were summarized using the mean (standard deviation [SD]) and median (range), and categorical variables were summarized using frequencies and proportions. All statistical analyses were performed using program SAS Enterprise Guide version 7.1.

## **RESULTS**

### **Caregiver Characteristics**

In total, 95 caregivers of pediatric patients with NF1-PN met the eligibility criteria and participated in the survey. Among caregivers responding to the survey, 88.4% were female (Table 1). The median (range) age of caregivers was 44.0 (18.0–70.0) years, and most (78.9%) reported being married or in a domestic relationship. White or Caucasian individuals made up the majority of caregivers in this study (85.3%), followed by those who were Hispanic, Latino, or of Spanish origin (9.5%). A total of 13.7% of caregivers had been diagnosed with NF1, and 10.5% had been diagnosed with PN. Nearly half (48.4%) of the caregivers reported having anxiety, while depression and obesity were also commonly reported (34.7% and 25.3%, respectively).

Approximately 40.0% of the caregivers were employed full-time, 18.9% were employed part-time, and 23.2% described themselves as homemakers. While 6.3% of caregivers indicated that COVID-19 had resulted in an increase

**Table 1** Characteristics among caregivers of pediatric patients with NF1-PN

Age (years)	<i>N</i> = 95
Median (range)	44.0 (18.0, 70.0)
Sex, <i>n</i> (%)	<i>N</i> = 95
Female	84 (88.4)
Male	11 (11.6)
Race/ethnicity, <i>n</i> (%) <sup>a</sup>	<i>N</i> = 95
White or Caucasian	81 (85.3)
Hispanic, Latino, or of Spanish origin	9 (9.5)
Asian or Pacific Islander	6 (6.3)
Black or African American	3 (3.2)
American Indian or Alaska Native	1 (1.1)
Geographical region, <i>n</i> (%)	<i>N</i> = 95
South	33 (34.7)
West	27 (28.4)
Midwest	21 (22.1)
Northeast	14 (14.7)
Caregiver diagnosed with NF1, <i>n</i> (%)	<i>N</i> = 95
No	82 (86.3)
Yes	13 (13.7)
Caregiver diagnosed with PN, <i>n</i> (%)	<i>N</i> = 95
No	85 (89.5)
Yes	10 (10.5)
Health conditions, <i>n</i> (%) <sup>a</sup>	<i>N</i> = 95
Anxiety	46 (48.4)
Depression	33 (34.7)
Obesity	24 (25.3)
Diabetes	5 (5.3)
Cancer	2 (2.1)
None of the above	35 (36.8)
Employment status, <i>n</i> (%) <sup>b</sup>	<i>N</i> = 95
Employed full-time	39 (41.1)
Homemaker	22 (23.2)

**Table 1** continued

Employed part-time	18 (18.9)
Self-employed	5 (5.3)
Long-term disability	4 (4.2)
Not employed, but looking for work	3 (3.2)
Not employed and not looking for work	2 (2.1)
Short-term disability	1 (1.1)
Student	1 (1.1)
Retired	0 (0.0)
Impact of the COVID-19 pandemic on employment status, <i>n</i> (%)	<i>N</i> = 95
No impact	42 (44.2)
Pay and/or hours were reduced	14 (14.7)
Lost job	8 (8.4)
Work increased	6 (6.3)
Not applicable	25 (26.3)
Marital status, <i>n</i> (%)	<i>N</i> = 95
Married or in a domestic partnership	75 (78.9)
Divorced or separated	14 (14.7)
Single, never married	4 (4.2)
Widowed	2 (2.1)

*NF1* neurofibromatosis type 1, *PN* plexiform neurofibromas

<sup>a</sup>Caregivers could have reported being in more than one category. Therefore, the sum of the percentages may exceed 100%

<sup>b</sup>Caregivers were asked to select the best option pertaining to their employment status at the time of survey administration

of work, another 23.1% reported job loss or reduced pay and/or hours due to the pandemic.

## Pediatric Patient Characteristics and Burden

To provide context to the results of the caregiver burden assessment, a brief description of the clinical characteristics and burden of the pediatric patient population with NF1-PN is described here (further details can be found in the publication by Yang et al. [28]). A total of 82 pediatric patients were included and the median age was 11.5 years. A majority (68.3%) of the study population had a diagnosis with NF1-PN for more than 5 years. One to two PNs were observed in most patients (71.9%) and 11.0% had more than five PNs. These PNs most frequently occurred on the back (40.2%) followed by the head (32.9%) and the spine (29.3%). The most prevalent NF1-PN symptoms reported included pain (64.6%) and disfigurement (32.9%). Patients were frequently reported to have comorbid conditions such as ADHD (56.1%), headaches (47.6%), and autism (18.3%). Among the 79 pediatric patients of school age, attention and learning problems were reported among the majority (79.0%). One or more debulking surgeries were reported among 39.0% of the pediatric population and 15.6% of these patients experienced surgical complications such as delayed healing and nerve damage. Pain relief medication was used as treatment among 31.7% of the population and 9.8% were treated with oncology medication such as cabozantinib, dabrafenib, imatinib, and vemurafenib.

The study indicated that pediatric patients with NF1-PN experience diminished overall health-related QoL (HRQoL) resulting from their disease. In addition to diminished HRQoL, pediatric patients experienced functional impairment across four domains: educational, emotional, social, and physical domains. Considerable pain (experienced by 64.6%) and motor dysfunction (28.0%) emerged as pressing concerns. Among pediatric patients reporting pain in the 7 days prior to answering the survey (ca. 50%), 74.2% reported moderate to severe pain as a result of their PN tumor(s).

**Table 2** Caregiver burden and work productivity and activity impairment among caregivers of pediatric patients with NF1-PN

ZBI <sup>a</sup>	<i>N</i> = 95
Burden score	
Mean (SD)	23.0 (13.8)
Median (range)	21.0 (0.0, 68.0)
WPAI:CG <sup>b</sup>	
Caregivers employed and working in the last 7 days	<i>N</i> = 56
Work hours missed in the past week due to child's NF1-PN	
Mean (SD)	2.4 (5.1)
Median (range)	0.0 (0.0, 25.0)
Absenteeism (%)	
Mean (SD)	6.9 (13.9)
Median (range)	0.0 (0.0, 67.6)
Presenteeism (%)	
Mean (SD)	17.3 (21.9)
Median (range)	10.0 (0.0, 80.0)
Work productivity Loss (%)	
Mean (SD)	22.3 (25.0)
Median (range)	10.0 (0.0, 85.5)
All caregivers	<i>N</i> = 95
Activity impairment (%)	
Mean (SD)	17.2 (22.5)

**Table 2** continued

Median (range)	10.0 (0.0, 100.0)
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*NF1* neurofibromatosis type 1, *PN* plexiform neurofibromas, *SD* standard deviation, *WPAI:CG* Work Productivity and Activity Impairment questionnaire, adapted for caregiving, *ZBI* Zarit Burden Interview

<sup>a</sup>For each of the 22 items, caregivers provided responses on a 5-point Likert scale ranging from 0 (never) to 4 (nearly always). The total score was the summation of the responses for each item and ranged from 0 to 88, with higher scores indicating greater burden associated with caregiving

<sup>b</sup>Impairment due to caregiving was measured over the past 7 days; absenteeism, presenteeism, and work productivity loss were measured only among caregivers working for pay. All scores are expressed as percentages

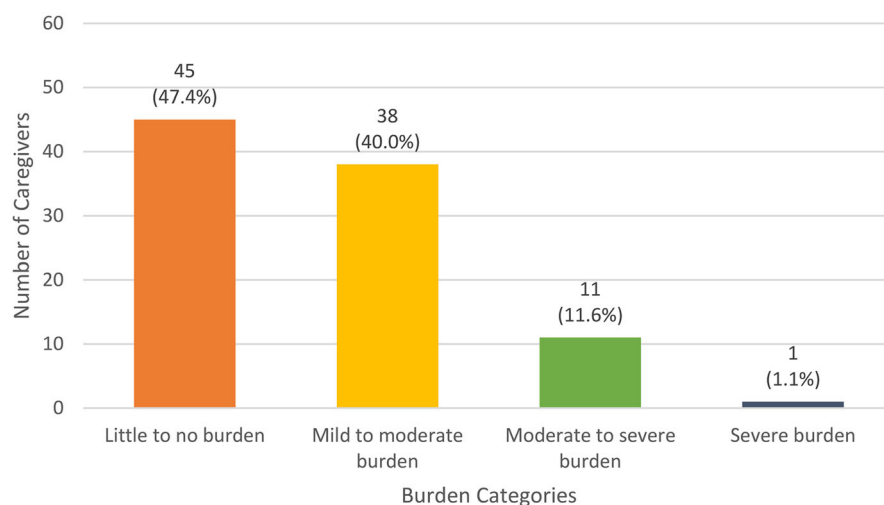
### Caregiver Burden

On the ZBI (higher scores = more burden), caregivers ( $N = 95$ ) reported a mean score of 23.0 ( $SD = 13.8$ ) on a scale from 0 to 88 (Table 2). Categorically, these scores suggest that 40.0% reported mild to moderate burden (scores 21–40) and 12.7% reported moderate to

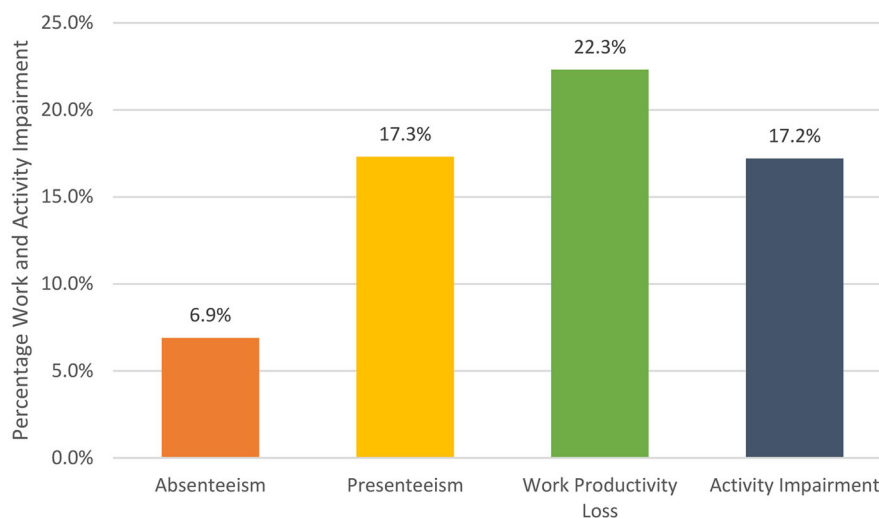
severe burden (scores 41–60) or severe burden (scores 61–88; Fig. 1).

### Work Productivity and Activity Impairment

Work productivity and activity impairment among caregivers based on the WPAI:CG is presented in Table 2 and Fig. 2. Among caregivers working for pay in the last 7 days ( $N = 56$ ), a mean of 2.4 ( $SD = 5.1$ ) hours of work was missed in the past week because of the child's NF1-PN. As a result of caring for their child with NF1-PN, employed caregivers reported missing an average of 6.9% ( $SD = 13.9\%$ ) of their working hours (absenteeism) and an average reduction of 17.3% ( $SD = 21.9\%$ ) of on-the-job effectiveness (presenteeism), contributing to an average of 22.3% ( $SD = 25.0\%$ ) of work productivity (i.e., the inability to fully attend work along with the inability to be effective during working hours) lost in the past week. Among the entire sample of caregivers ( $N = 95$ ), an average of 17.2% ( $SD = 22.5\%$ ) of regular daily activities other than working at a job were hindered by providing care for their child with NF1-PN (activity impairment).



**Fig. 1** Caregiver burden based on the ZBI. *ZBI* Zarit Burden Interview



**Fig. 2** Caregiver work productivity and activity impairment based on the WPAI:CG. WPAI:CG Work Productivity and Activity Impairment questionnaire, adapted for caregiving. Absenteeism, presenteeism, and work

productivity loss were only assessed among the 56 patients who were employed and working in the 7 days prior to answering the survey. Activity impairment was assessed among all caregivers

## DISCUSSION

This real-world study was one of the first to characterize the burden among caregivers of pediatric patients with NF1-PN in the USA. Based on the results of this cross-sectional survey, the burden among caregivers of pediatric patients with NF1-PN was considerable, amounting to about one-fifth of overall loss in work productivity (i.e., diminished effectiveness at work along with the inability to attend work for the job-required number of hours) and daily activities impairment. Moreover, approximately 50% of caregivers reported burden ranging from mild-to-moderate to severe. The results of the present study highlight that the burden of NF1-PN extends beyond the burden incurred by pediatric patients, underscoring an unmet need for better management of NF1-PN.

These findings build upon prior literature showing a substantial burden among caregivers of pediatric patients with chronic conditions [19–22, 24]. A prior study measuring overall burden using the ZBI by Javalkar et al. found that caregivers of children with chronic conditions had a high degree of perceived burden [19]. Prior evidence has also indicated marked productivity losses among caregivers that are

especially pronounced among those caring for pediatric patients. In a study by King-Stephens et al. [20], WPAI:CG scores were higher among caregivers of chronically ill children (6 months–11 years of age) and adolescents (12–17 years of age) relative to caregivers of chronically ill adults (at least 18 years of age). Specifically, parents of chronically ill children had the highest mean percentage of overall productivity loss (55%), lowest employment rates (33%), and disruption of regular activities “some of the time” (90% of respondents) and “all of the time” (55% of respondents) [20]. Studies assessing indirect economic burden have noted a considerable impact of caregiving by this metric. In a study of 1711 adolescents (aged 12–17 years old) with chronic pain identified from the 2016 National Survey of Children’s Health, 15% of parents reported spending at least 1 h/week on their child’s healthcare, 14% reported cutting back on paid work in the past 12 months [22]. Other studies have reported a similarly high indirect economic burden among caregivers of chronically ill children in the USA and Europe [23, 24].

Mental and physical health conditions were highly prevalent among caregivers of pediatric patients with NF1-PN in the present study, with



nearly 50% self-reporting anxiety and nearly 35% self-reporting depression. This is largely consistent with prior studies reporting high rates of self-reported distress, anxiety, and depression among caregivers of pediatric patients [20, 24–27]. Among caregivers of children with NF1, Wiener et al. [27] found 12.5% met criteria for a “case” on the somatization subscale of the Brief Symptom Inventory (BSI-depression items; BSI-18), including 11.3% for anxiety, 3.8% for depression, and 8.8% for the Global Severity Index. Similarly, King-Stephens et al. [20] found that caregivers of chronically ill children bore a heavy physical and emotional burden (a mean number of overall [physically + mentally] unhealthy days of  $N = 16.9$  days per month), with a high proportion of respondents experiencing frequent distress (47.1%) as defined by the US Centers for Disease Control and Prevention. Although one cannot infer a causal link between mental health conditions and caregiver burden in the present study, emotional distress and anxiety have been shown to be positively correlated with caregivers’ feeling of burden in a prior study [25]. Furthermore, the degree of caregiver burden based on ZBI may also be a robust independent predictor of depression and anxiety [26]. Taken together, this evidence suggests a complex relationship between psychological/emotional factors and burden among caregivers of chronically ill pediatric patients.

Prior literature on caregivers of children with other chronic conditions has shown that certain factors indicative of greater disease severity and complexity can drive caregiver burden [22, 34]. Such factors are often present in NF1-PN and may therefore account for the high burden experienced by caregivers of pediatric patients in the present study. For instance, Javalkar et al. [19] found that the caregiver burden was likely to be higher among parents of children with a greater number of medicines and injections, a diagnosis of comorbid ADHD, and frequent healthcare resource utilization (HRU). In a separate publication by the present authors, caregivers in the current dataset had described similar characteristics among the pediatric patients with NF1-PN who were in their care. Specifically, this study found that

approximately 30% of pediatric patients with NF1-PN had received pain medications and 56% had ADHD, while high HRU was observed among patients who had undergone debulking surgeries [28]. The extent to which the central nervous system is involved in a pediatric patient’s NF1-PN may also impact caregiver burden. One study found that children with NF1 who had greater neurological involvement also had more severe emotional and social problems from the perspectives of their peers and parents [35]. These more severe neurocognitive challenges among certain patients with NF1 may in turn lead to more demanding caregiver responsibilities as well as a greater perceived burden [35, 36]. These findings emphasize the need for future studies characterizing the burden experienced by caregivers, including correlations and associations, particularly in relation to patient characteristics that may potentially exacerbate this burden.

Finally, approximately 30% of the participating caregivers in this study experienced job-related impacts due to the COVID-19 pandemic, such as loss of employment, reduction in salary, or increase in work hours. Additionally, nearly 75% of school-going children transitioned to a fully remote or hybrid learning model during this time. Given these reported changes in employment and education, the COVID-19 pandemic may have exacerbated caregiver burden.

## Limitations

The present findings should be considered within the context of certain limitations. First, this self-report study may have been subject to recall bias, which occurs when a caregiver’s response depends on their ability to precisely recall past events (e.g., work hours missed in the past week due to child’s NF1-PN). Because the present study relied on widely used and/or validated self-report instruments such as WPAI:CG, the impact of recall bias was likely minimized. Although the self-report instruments used in this study have not been validated specifically among caregivers of patients with NF1-PN, they have been used and/or

validated in caregiver populations of patients with other chronic conditions. In particular, the ZBI instrument had been used but not validated among caregivers of pediatric patients with chronic conditions, including cancer, Down syndrome, craniofacial anomalies, and spina bifida [19, 25, 31]. The WPAI instrument had been validated across informal caregivers of chronically ill patients [33], but had not been validated in caregivers of patients with NF1-PN. Of note, caregiver burden as measured in terms of work productivity is agnostic to the disease of the patients; therefore, the absence of validation studies in NF1-PN is not likely to be a limiting factor for this outcome. As with any retrospective observational self-report study, there is generally the potential for missing or inaccurate data. Third, the results obtained in the present study may not be generalizable to all caregivers of pediatric patients with NF1-PN (e.g., non-US residents, non-English speakers). Respondents who agreed to participate in the present survey may be different from non-respondents and there may be self-selection bias which is inherent in convenience samples. Furthermore, the pediatric patients of these caregivers have been restricted to those who are treatment naïve or treated with selumetinib and excludes those who were treated with other off-label treatments. This may have resulted in the selection of an NF1-PN patient population with less severe illness relative to the overall population with NF1-PN. Finally, this study did not capture the granular details of each pediatric patient's PN, and as a result, correlations could not be calculated between the burden experienced by the caregiver with the clinical manifestations or the severity of their pediatric patient's NF1-PN.

## CONCLUSION

The present cross-sectional study assessed the self-reported burden among primary caregivers of pediatric patients with NF1-PN in the USA. The findings indicate that caregivers experienced a substantial overall burden based on ZBI scores, indicating an impact across multiple domains including physical, psychological,

economic, and social ones. Moreover, caregivers reported considerable work productivity losses and impairment of daily activities based on the WPAI:CG. These results highlight an urgent unmet need to alleviate the humanistic and clinical disease burden among pediatric patients with NF1-PN, and to further characterize the burden among their caregivers, with the aim of improving QoL. Future studies are needed to improve the understanding of caregiver burden, including correlations and associations to identify specific factors impacting burden.

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and Lujia Zhang. All authors reviewed and approved the paper.

**Disclosures.** Xiaoqin Yang is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and owns stock in Merck & Co., Inc., Rahway, NJ, USA. Hyun Kyoo Yoo is an employee of AstraZeneca and owns stock. Suvina Amin was an employee of AstraZeneca and owned stock during the conduct of this study. Wendy Y. Cheng, Sanjana Sundaresan, Lujia Zhang, and Mei S. Duh are employees of Analysis Group, Inc., which received funding from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, in collaboration with AstraZeneca UK Limited for the conduct of the present study.

**Compliance with Ethics Guidelines.** This retrospective survey study was conducted in accordance with the ethical standards of the Declaration of Helsinki. The study was approved by the WCG IRB (reference number 20202853). All participants signed an informed consent form regarding the publication of the data they contributed to this study.

**Data Availability.** The analytical datasets used in this study are available from the corresponding author upon reasonable request.

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