

Patient- and Caregiver-Reported Quality of Life and Burden of Disease in Wiskott-Aldrich Syndrome: Findings from a Multinational Survey

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BACKGROUND

Wiskott-Aldrich Syndrome (WAS)

- A rare X-linked primary immunodeficiency caused by mutations in the WAS gene expressed exclusively in hematopoietic cells¹
- Characterized by microthrombocytopenia, eczema, recurrent infections, and an increased incidence of autoimmunity and malignancies¹
- There are two main types of WAS: Classic WAS and X-linked thrombocytopenia (XLT)—Classic WAS is characterized as a more severe phenotype while XLT patients typically experience milder symptoms (e.g., fewer problems with eczema and infections)²
- Despite presenting as a milder phenotype, XLT is a progressive disease that may develop autoimmunity and/or malignancies and convert to Classic WAS over time³
- Currently, despite its limitations, hematopoietic stem cell transplant (HSCT) is considered the treatment method of choice for WAS⁴

Objective

- This multinational study aims to quantify both the caregiver and patient-related burdens of WAS and add to the existing literature by examining various domains of health-related QoL including symptom burden, transplant burden, time investment, social and emotional well-being, and professional status
- Understanding disease impact for transplanted vs. non-transplanted patients and based on time since transplant were also key metrics of exploration to uncover any long-term impacts of HSCT

RESEARCH METHODOLOGY

Inclusion/Exclusion Criteria

- Must have a diagnosis of WAS or be the primary caregiver of WAS patient(s)
- Patients who have received investigational gene therapy were excluded

Quantitative Survey and PedsQL Questionnaire

- Survey was validated by WAS clinical experts and patient advocacy group representatives and obtained information on caregiver and patient demographics, symptom burden, treatment burden, time investment, social and emotional well-being, professional status and finances
- PedsQL questionnaire⁵ was completed to measure health-related quality of life (HRQoL) of WAS patients; The scores of the PedsQL ranges from 0 to 100 with higher scores indicating higher HRQoL
- Survey and questionnaire were administered by moderator
- Study protocol and survey also received IRB approval

Qualitative Interview and EQ-5D-5L Questionnaire

- Follow-up qualitative discussions conducted to discuss survey responses in-depth
- EQ-5D questionnaire was completed to measure the HRQoL of caregivers or patients (depending on respondent type)

DEMOGRAPHICS

- The study included 20 caregivers in the US (13), UK (4), Germany (2) and Canada (1)
- The caregivers reported on a total of 22 individuals with WAS, with one caregiver in the US and one caregiver in Germany reporting on two children diagnosed with WAS
- Additionally, the study included three adult WAS patients in the US, UK and Germany who self-reported; breakdowns of self-reported data have been omitted due to small sample size
- Overall, the study included data on 25 WAS patients – majority of patients were classified as Classic WAS (72.0%) versus XLT
- Sixteen patients (64.0%) had received stem cell transplant; data was also analyzed based on time since transplant (<5 years vs. > 5 years since transplant)

Table 1: Caregiver Sample Characteristics

	Total	US/CA	UK	DE
N	20	14	4	2
Mother of child with WAS	100.0%	100.0%	100.0%	100.0%
Age, years Median (range)	40.0 (22.0 - 58.0)	40.0 (22.0 - 58.0)	38.5 (36.0 - 42.0)	40.5 (33.0 - 48.0)
Living with partner	15 (75.0%)	12 (85.7%)	1 (25%)	2 (100%)
Employed full-time	6 (30.0%)	5 (35.7%)	1 (25.0%)	2 (100%)

Table 2: Patient Sample Characteristics

	Total N	US/CA	UK	DE
N	25	16	5	4
Gender, male	100%	100%	100%	100%
WAS classification, Classic	18 (72.0%)	11 (68.8%)	5 (100%)	2 (50.0%)
WAS classification, XLT	7 (28.0%)	5 (31.3%)	—	2 (50.0%)
Median current age, years (range)	11.5 (1.5 - 51.0)	10.6 (1.5 - 29.4)	7.8 (1.9 - 48.2)	15.8 (2.4 - 51.0)
Median age at WAS diagnosis, months Median (range)	8.0 (0.0 - 60.0)	11.0 (0.0 - 60.0)	7.0 (3.0 - 14.0)	6.0 (0.0 - 60.0)
Number of patients who received transplant	16	10	5	1
Time since transplant, years median (range)	5.3 (0.7 - 21.8)	5.3 (0.7 - 18.4)	6.6 (0.8 - 21.8)	—
Subgroup: < 5 years since transplant, N	8	5	2	1
Subgroup: ≥5 years since transplant, N	8	5	3	—

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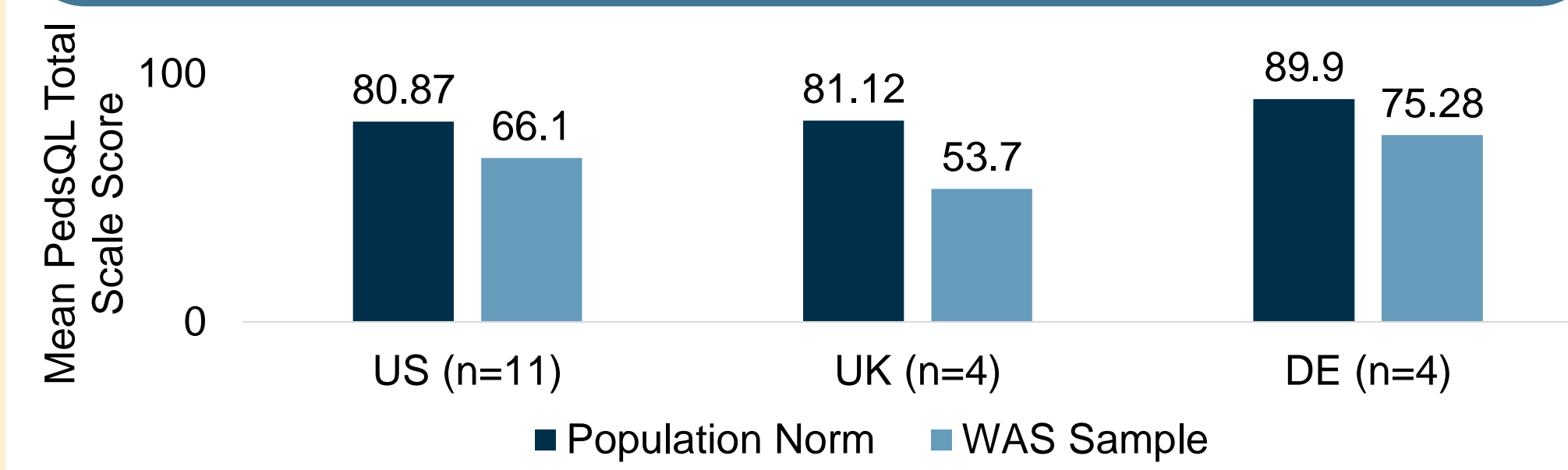
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RESULTS: IMPACT OF WAS ON PATIENTS

PedsQL™ Quality of Life

- HRQoL of WAS patients in the US, UK, and DE samples were directionally lower than that of the respective population norms according to PedsQL scores
- From a **physical impact** perspective, respondents most commonly reported 'sometimes', 'often', or 'almost always' having problems with participating in sports (60.0%), having hurts or aches (60.0%), and/or having low energy level (60.0%) in the previous 4-week period
- The greatest delta compared to population norms on **psychosocial health** summary scores was WAS patients' frustrations from not being able to do things their peers can do. Psychosocial health scores ranged from 6.8 to 28.7 points lower for WAS sample compared to population norms

Figure 1: PedsQL 4.0 Generic Core Total Scale Scores – WAS Sample vs. Population Norms

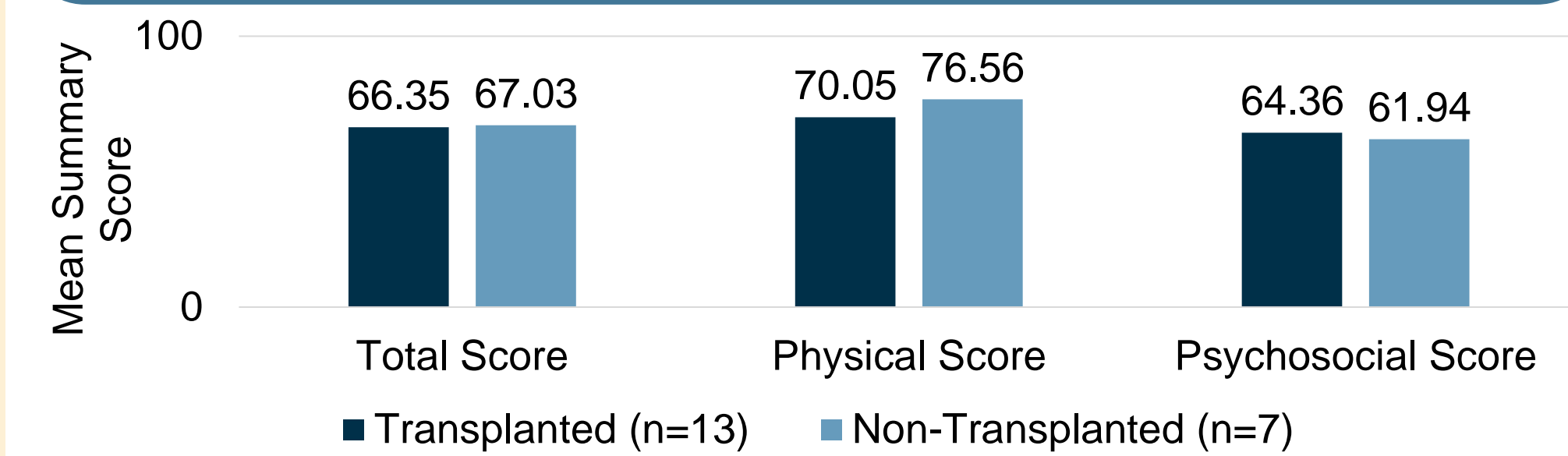


**Population norms for US (n=1622)⁶ and UK (n=970)⁷ were based on proxy reports for a mix of ill and healthy patients; DE (n=491)⁵ population norms based on a "healthy" cohort; data not included for CA due to small n

Subgroup Analyses

- Despite variability in symptom severity in Classic WAS versus XLT, both phenotypes exhibited similar degrees of health-related quality of life impacts based on the PedsQL (total scale score of 64.62 versus 67.7 respectively)
- PedsQL scores were comparable for patient who had and had not received transplant—66.35 mean summary score for transplanted patients versus 67.03 for non-transplanted patients

Figure 2: PedsQL 4.0 Generic Core Total Scale Scores – Transplanted vs. Non-Transplanted Patients



Symptom Burden

Table 3: Percent of WAS Patients Whose Symptoms "Moderately to Extremely" Impacted QoL

In past 4 weeks...	Transplant Patients (n=16)	Non-transplant Patients (n=9)	<5 Years Since Transplant (n=8)	≥5 Years Since Transplant (n=8)
Excessive Tiredness	18.8%	55.6%	12.5%	25.0%
Rash/eczema	25.0%	44.4%	37.5%	12.5%
Easy bruising	6.3%*	77.8%*	12.5%	0.0%
Upper respiratory infection	25.0%	33.3%	0.0%	50.0%
Learning difficulties	37.5%	0.0%	50.0%	25.0%
Other autoimmunity	18.8%	0.0%	12.5%	25.0%
Recurrent infections	12.5%	33.3%	12.5%	12.5%

*Statistically significant difference (P <0.05) between proportion of transplant vs. non-transplant patients

Subgroup Analyses

- Expected nuances in disease manifestations for Classic WAS and XLT patients emerged with 57% of XLT patients reporting petechiae having moderate to extreme impact on patients' life versus 6% of Classic WAS patients (p = 0.012)
- Impact of easy bruising on QoL is the only symptom which was significantly higher amongst non-transplant patients compared to transplant patients (p < 0.001)
- Time since transplant had no significant difference in symptoms' impacts on QoL—while more recently transplanted patients were directionally more likely to experience rash/eczema and learning difficulties, those 5+ years since transplanted were directionally more likely to report impacts from upper respiratory infections and other autoimmunity

"Moderate or Extreme" Impact on Social Activities in Previous 4-Week Period (n=25)

- The **physical health** of most WAS patients (60.8%) interfered with their ability to participate in social activities (46.7% transplant vs. 87.5% non-transplant patients, p=0.086)
- The **risk of bleeding** interfered with social activities for 50.0% of WAS patients (20.0% transplant vs. 100% non-transplant patients, p<0.001)
- The **risk of infection** interfered with social activities for 72.0% of WAS patients (62.5% transplant vs. 88.9% non-transplant patients, p=0.355)

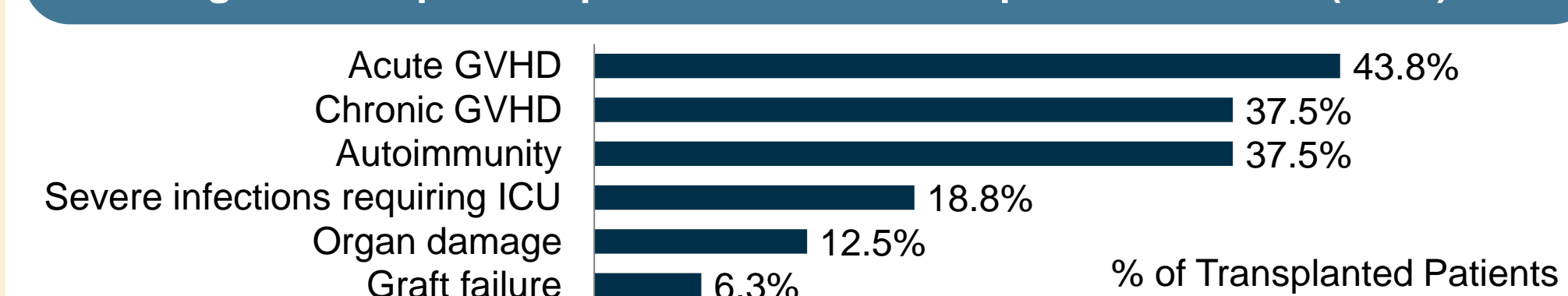
Subgroup Analyses

- Non-transplanted patients reported a significantly higher interference of risk of bleeding on social activities (p = 0.028)
- There was no significant difference in impact of social activities for those greater than versus less than 5 years since transplant

Transplant Burden

- 93.8% of transplant patients experienced a **transplant-related complication**, 56% of patients experienced some extent of GVHD post-transplant (chronic, acute, or both)
- Autoimmunity** still negatively impacts the QoL of 33% of the patients quite a bit/extremely (n=6)
 - One of the two patients reporting current impacts on QoL from autoimmunity was 5+ years since transplant
- Chronic GVHD** still negatively impacts the QoL of 50% of the patients quite a bit/extremely (n=6, moderate to extreme impact)
 - One of the three patients reporting current impacts on QoL from cGVHD was 5+ years since transplant

Figure 3: Top 5 Complications from Transplant Procedure (n=16)



Time Investment

- Median number of WAS-related outpatient visits in the previous 12-month period was **8.0 visits** across all families

Subgroup Analyses

- Differences between the median number of outpatient visits per year for transplant vs. non-transplant patients were not statistically significant
- Time since transplant had no statistical significance on median number of outpatient visits per year, although those who were within 5 years since transplant had directionally more annual outpatient visits

Table 4: Median Number of Outpatient Visits in the Previous 12-Month Period

	Transplant Patients (n=16)	Non-transplant Patients (n=9)	<5 Years Since Transplant (n=8)	≥5 Years Since Transplant (n=8)
Outpatient visits	8.5 (1.0–144.0*)	8.0 (0–50.0)	18.0 (1.0–144.0*)	3.0 (2.0–40.0)

*Patient with 144 outpatient visits had received stem cell transplant in the past year

RESULTS: IMPACT OF WAS ON CAREGIVERS

"Often or Always" Worried in Previous 4-Week Period (n=20)

- 83% of caregivers of non-transplanted patients reported being worried about their child's **risk of infection** compared to 29.0% of caregivers of transplant (p = 0.02) -- About half of caregivers (45.0%) reported concern overall
- 33.0% of caregivers of non-transplanted patients reported worries around their child's **risk of bleeding** versus 0% of caregivers of transplanted children (p = 0.02) – 10.0% of caregivers report this worry overall

Subgroup Analyses

- Caregivers of non-transplanted patients reported a significantly higher rate of worry of risk of bleeding and risk of infection than caregivers of transplanted patients
- Time since transplant had no significant difference on caregiver's rate of worry of risk of infection

Psychological Impact in Previous 4-week Period

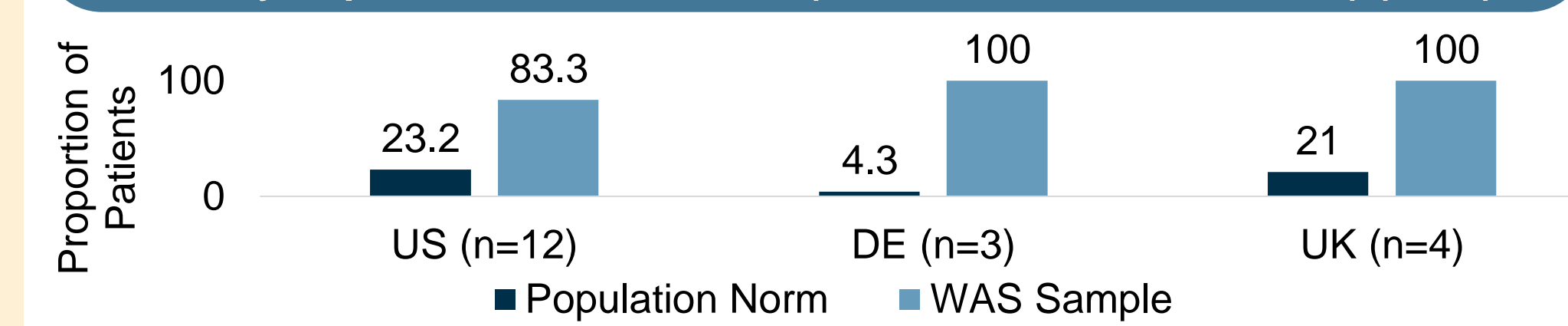
- 80.0% of caregivers had "quite a bit" or "a great deal" of **concern about their child's future** (n=20)
- 81.0% of caregivers had "quite a bit" or "a great deal" of **concern about the emotional/psychological impact of WAS on their child's siblings** (n=16*)

*only includes caregivers who have another child/children

Subgroup Analyses

- Despite transplant, 71% of caregivers of transplanted patients (n=14) are still concerned about what their child's future is likely to be

Figure 4: Proportion of Caregivers Reporting Problems with Anxiety/Depression in Past Month (EQ-5D-5L Dimension Score) (n=19)



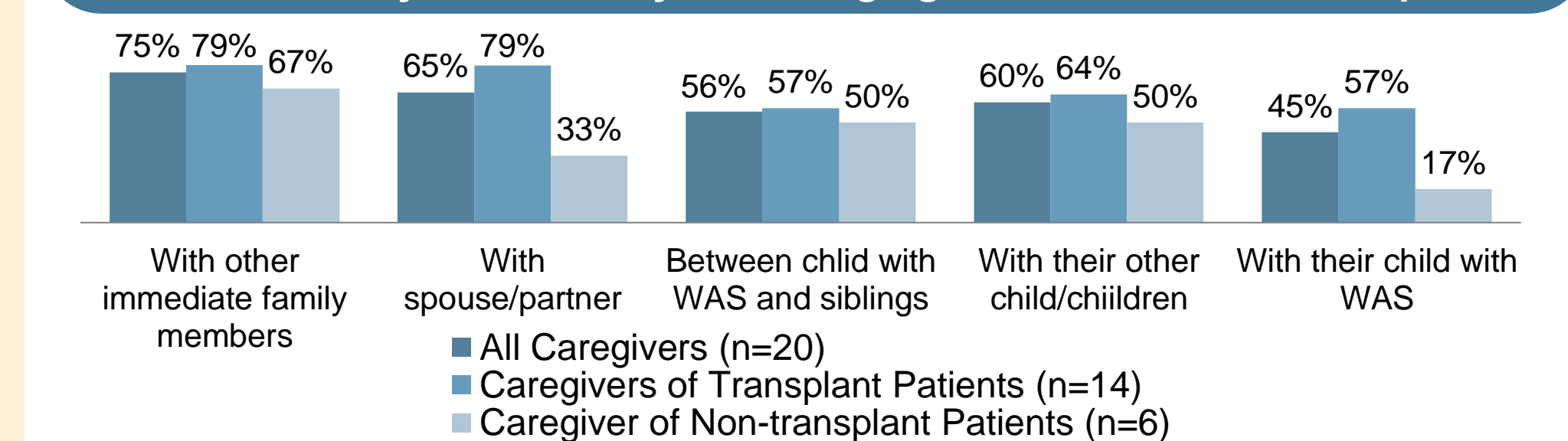
EQ-5D-5L results indicate caregivers of WAS patients experience more problems with **anxiety and depression** compared to population norms (p<0.05 across US, DE, and UK)

- The majority of caregivers surveyed (79.0%) reported that they had received mental health support (85.0% transplanted vs. 67.0% non-transplanted patients, p=0.37)

Familial and Social Impact (n=20)

- Caregivers' **relationships with their spouse/partner and other immediate family** members were most negatively impacted by WAS
- A directionally higher proportion of caregivers of transplanted patients (78.5%) reported that their relationship with their spouse/partner had been negatively impacted by WAS (vs. 33.3% non-transplant; p = 0.078)

Figure 5: Proportion of Caregivers Reporting That WAS Made It "Moderately to Extremely" Challenging to Maintain Relationships



Professional Impact

- 60% of caregivers report having to **stop working** at some point to be able to provide care for their child with WAS (71% transplant, 33% non-transplant; p=0.11)
- Median length of time out of work for those who had to stop (n=12) was 3.3 years
- A higher proportion of caregivers of non-transplant patients (66.7%) have had to **miss work** to provide care to their child with WAS (vs 28.6% transplant; p=0.161)

DISCUSSION

- This multinational study highlights the impact of WAS both on patients and caregivers
- Overall, individuals with WAS experience a poorer HRQoL compared to the general population based on directional results from the PedsQL
 - The burden of disease can manifest in different ways including symptom burden, treatment burden and time investment with healthcare visits
- While the impact of WAS on transplanted patients' QoL is less pronounced compared to non-transplanted patients, many caregivers and patients report a continued impact on QoL such as the burden of ongoing symptomatic treatments, learning difficulties, and complications from the transplant procedure itself
 - Even after the transplant process, families have to interact regularly with healthcare providers and patients visit a physician outpatient around 8 times a year
- When looking at families of more recently transplanted patients (i.e., <5 years since transplant), and those many years post transplant, there are minimal significant differences in quality of life profiles, indicating the long-term implications and QoL burdens despite transplant
 - Symptom burden and interference with social activities were comparable with most directional differences in the number of annual outpatient visits
- For caregivers, the psychological and financial impact are evident—many are left with a persistent concern for their child's future, regardless of treatment received and several report needing to stop work or miss work to take care of their child with WAS
 - Caregivers also often worry about the impact on their other children
- In conclusion, this study underscores the direct and indirect impact of WAS on families, and the need for continued advancement in treatment options

DISCLOSURES/DISCLAIMERS

- This research was sponsored and funded by Orchard Therapeutics, Ltd., London, UK and was designed through a collaboration between the sponsor and Magnolia Innovation, LLC, Hoboken, NJ.
- F. Pang and A. Dillon are previous or current employees of the sponsor, Orchard Therapeutics, Ltd.
- A. Wilds, A. Afriyie, M. Walz, and K. Howie, K. Lanier are previous or current employees of Magnolia Innovation, LLC.

ACKNOWLEDGMENTS

- The researchers would like to thank the study respondents and their families as well as patient advocacy organizations for their support and input including: WAS Foundation, Immunodeficiency UK, and DSAI
- The authors gratefully acknowledge the contribution of the caregivers and patients who participated in the study