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Complete List of Authors:	Simonelli, Francesca; University of Campania "L. Vanvitelli, Eye Clinic, Multidisciplinary Department of Medical, Surgical and Dental Sciences Sodi, Andrea; University of Florence, Department of Neuroscience, Psychology, Drug Research and Child Health Falsini, Benedetto; Fondazione Policlinico Universitario Agostino Gemelli IRCCS, UOC Oftalmologia Bacci, Giacomo; Children's Hospital A. Meyer, University of Florence, Pediatric Ophthalmology Unit Iarossi, Giancarlo; Bambino Gesù IRCCS Pediatric Hospital, Ophthalmology Department Di iorio, Valentina; University of Campania "L. Vanvitelli", Eye Clinic, Multidisciplinary Department of Medical, Surgical and Dental Sciences Giorgio, Dario; University of Florence, Department of Neuroscience, Psychology, Drug Research and Child Health Placidi, Giorgio; Fondazione Policlinico Universitario Agostino Gemelli IRCCS, UOC Oftalmologia Andrao, Assia; Retina Italia Onlus Association Reale, Luigi; ISTUD Foundation Fiorencis, Alessandra; Fondazione ISTUD, Aoun, Manar; Novartis Farma SpA Vitiello, Giovanni; University of Campania "L. Vanvitelli", Eye Clinic, Multidisciplinary Department of Medical, Surgical and Dental Sciences Citro, Amelia; University of Campania "L. Vanvitelli", Eye Clinic, Multidisciplinary Department of Medical, Surgical and Dental Sciences De Simone, Simona; University of Campania "L. Vanvitelli", Eye Clinic, Multidisciplinary Department of Medical, Surgical and Dental Sciences De Rienzo, Irene; Careggi University Hospital - Florence, Italy , Department of Ophthalmology Filimonova, Natalia; Novartis Pharma AG Fortini, Stefania; Fondazione Policlinico Universitario Agostino Gemelli IRCCS, National Center of Services and Research for the Prevention of Blindness and Rehabilitation of the Visually Impaired, WHOCC ITA-100 Marchese, Cristiana; Retina Italia Onlus Association Marini, Maria Giulia; Fondazione ISTUD, Healthcare Area Mucciolo, Dario Pasquale; University of Florence, Murro, Vittoria; University of Florence, Department of Neuroscience, Psychology, Drug Research and Child Health Passerini, Ilaria; Careggi Teaching Hospital, Department of Genetic

	Diagnosis Turco, Simona; Fondazione Policlinico Universitario Agostino Gemelli IRCCS, National Center of Services and Research for the Prevention of Blindness and Rehabilitation of the Visually Impaired, WHOCC ITA-100
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Narrative Medicine to investigate the quality-of-life and emotional impact of RPE65-related inherited retinal disorders through the perspectives of patients, caregivers, and clinicians: an Italian multicentre project.

Francesca Simonelli[1], Andrea Sodi[2], Benedetto Falsini[3,4], Giacomo Bacci[5], Giancarlo Iarossi[6], Valentina Di Iorio[1], Dario Giorgio[2], Giorgio Placidi[3,4], Assia Andrao[7], BIRDS Working Group, Luigi Reale[8], Alessandra Fiorencis[8], Manar Aoun[9]

BIRDS Working Group: Giovanni Bosco Vitiello[1], Amelia Citro[1], Simona De Simone[1], Irene De Rienzo[10], Natalia Filimonova[11], Stefania Fortini[12], Cristiana Marchese[7], Maria Giulia Marini[8], Dario Pasquale Mucciolo[2], Vittoria Murro[2], Ilaria Passerini[13], Simona Turco[12]

[1] Eye Clinic, Multidisciplinary Department of Medical, Surgical and Dental Sciences, University of Campania "L. Vanvitelli" – Naples, Italy

[2] Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence – Florence, Italy

[3] UOC Oftalmologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

[4] Università Cattolica del Sacro Cuore, 00168 Rome, Italy

[5] Pediatric Ophthalmology Unit, Children's Hospital "A. Meyer", University of Florence – Florence, Italy

[6] Ophthalmology Department, Bambino Gesù IRCCS Pediatric Hospital – Rome, Italy

[7] Retina Italia Onlus Association – Italy

[8] Healthcare Area, Fondazione ISTUD – Milano, Italy

[9] Novartis Farma – Origgio, Italy,

[10] Department of Ophthalmology, Careggi University Hospital - Florence, Italy

[11] Novartis Pharma AG – Basel, Switzerland

[12] National Center of Services and Research for the Prevention of Blindness and Rehabilitation of the Visually Impaired, WHOCC ITA-100/Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy

[13] Department of Genetic Diagnosis, Careggi Teaching Hospital – Florence, Italy

*Corresponding authors: Luigi Reale, Healthcare Area, Fondazione ISTUD – via Paolo Lomazzo 19, 20124 Milano, Italy. Tel. +39 0323 933 801, Mobile +39 3484759910, e-mail: lreale@istud.it

Francesca Simonelli, University of Campania "L. Vanvitelli" – via S. Pansini 5, 80131. Tel. +39 081 5666607, e-mail: francesca.simonelli@unicampania.it

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ABSTRACT

Objectives. Although inherited RPE65-related retinal disorders (IRDs) significantly impact the vision-related quality of life (VRQoL), their emotional and social aspects remain poorly investigated in Italy. Narrative Medicine (NM) reveals the more intimate aspects of the illness experience, providing insights into clinical practice.

Design and setting. This NM project was conducted in Italy between July and December 2020 and involved five eye clinics specialised in IRDs. Illness plots and parallel charts, together with a sociodemographic survey, were collected through the project's website; in-depth interviews were also conducted. Narratives and interviews were analysed through Nvivo software and interpretive coding.

Participants. Three paediatric and five adult patients and eight caregivers participated in the project; 11 retinologists globally wrote 27 parallel charts; five professionals from hospital-based multidisciplinary teams and one Patient Association member were interviewed.

Results. Findings confirmed that RPE65-related IRDs impact VRQoL in terms of activities and mobility limitations. The emotional aspects emerged as crucial in the clinical encounter and as informative on IRD management challenges and real-life experiences, while psychological support was addressed as critical from clinical diagnosis throughout the care pathway for both patients and caregivers; the need for an IRDs "culture" emerged to acknowledge these conditions and therefore promoting diversity within society.

Conclusions. The project was the first effort to investigate the impact of RPE65-related IRDs on the illness experience through NM, concomitantly addressing the perspectives of paediatric and adult patients, caregivers, and healthcare professionals and provided preliminary insights for the knowledge of RPE65-related IRDs and the clinical practice.

Keywords: inherited retinal dystrophies, *RPE65* gene, narrative medicine, illness experience, quality of life

STRENGHTS AND LIMITATIONS OF THIS STUDY

- Inclusion of paediatric and adult patients' and hospital-based multidisciplinary team professionals' perspectives.
- Narrative Medicine approach.
- Preliminary findings to be investigated with further studies.

INTRODUCTION

Affecting about 1 in 2-3,000 people globally [1], Inherited Retinal Disorders (IRDs) constitute a group of clinically and genetically heterogeneous degenerative conditions in which gene mutations affect the proteins necessary to functional vision [2]. A progressive loss of photoreceptor cells and an impairment of the visual function characterise the IRDs related to mutations involving the RPE65 gene and gradually lead to an irreversible visual decline [3], and potentially to blindness [4]; Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP) represent the most common forms [5,6]. Age of onset ranges from early childhood to middle age; visual impairment at low light levels, night blindness and nystagmus are the early symptoms, followed by an increasing deterioration of visual acuity and peripheral vision [7]. While gene therapy represents a promising scenario for treating these conditions [3,8], IRDs management has been mainly support-oriented and focused on monitoring, counselling, and education [3].

RPE65-related IRDs significantly impact patients in daily activities [9], with implications for their sense of identity [10] and autonomy management [11]; previous studies associate visual impairment with lower social engaging ability [12], self-confidence and vision-related quality of life (VRQoL) [13], as well as with higher levels of depression [14,15].

Against this backdrop, other studies [16,17] suggest that a holistic and multidisciplinary approach – also addressing IRDs emotional and social aspects – is crucial to support patients and their caregivers.

The World Health Organisation (WHO) has acknowledged narrative research as informative to address the illness experience [18] in leading clinical practice [19]; a keen focus on narratives resulted in better patient care also in clinical genetics practice [20]. As described in similar studies [21], Narrative Medicine (NM) is based on illness narratives [22] and aims to integrate the *disease*-centred approach, related to the biomedical sphere, with the *illness*- and *sickness*-centred approaches, focusing on the individual and social experience of a condition [23], respectively. NM addresses the possible interventions on a specific disorder by integrating the perspectives of all the actors involved in the care pathway [24], and its findings have been increasingly used to improve the quality of care in clinical practice [25,26].

The NM project "BIRDS – The Beat of IRD Stories" investigated the RPE65-related IRDs illness experience through the analysis of narratives (a) to reveal the practical, emotional, and social issues linked to these conditions as experienced by patients, caregivers, and healthcare professionals, and (b) to understand the patient's journey and expectations regarding the gene therapy, to finally provide insights to foster the knowledge on RPE65-related IRDs and clinical practice.

The present research article focuses on the first goal (a); another study addressed the second one [27]. Although other studies integrated the perspectives of both patients and caregivers [28, 29], to the best of our knowledge, this is the first project that also engages the retinologists and hospital-based multidisciplinary professionals (MDTs) in investigating the RPE65-related IRDs illness experience.

METHODS

Research design and setting

The project was conducted in Italy between July and December 2020 and targeted paediatric and adult patients with an RPE65-related IRD, their caregivers, retinologists and MDT professionals involved in their care pathway. Participants were enrolled from five eye clinics specialised in IRDs (Supplementary file 1) across Italy. In July 2020, the Steering Committee – composed of five retinologists working in these centres and a Patient Association (PA) member – participated in an online meeting conducted by researchers from ISTUD Foundation to be trained in NM and to discuss the project's goals and design; the Steering Committee, together with other IRD specialists from these centres, were then invited to engage patients and caregivers in participating in the research by accessing the project's webpage http://www.medicinanarrativa.eu/birds.

A clinical RPE65-related IRD diagnosis or the caregiving of a person with an RPE65-related IRD constituted the eligibility criteria for patients and caregivers, as well as the willingness to share their illness experience; however, the ability to write or communicate in Italian was critical for the inclusion.

Data collection

Researchers followed the Web Content Accessibility Guidelines (WCAG) 2.1 [30] to ensure survey accessibility. Patients were invited to share their narratives either by writing or recording an audio file; also, caregivers were allowed to support paediatric patients in writing. Narratives were anonymously collected through the Alchemer platform, available on the project's webpage. Afterwards, raw narratives were downloaded as Microsoft Excel spreadsheets.

A sociodemographic survey and an illness plot [31] were addressed to patients and caregivers; evocative and open words characterised the illness plot to facilitate individual expression [32] and chronologically guide the narrative to identify changes over time. The retinologists' caring experience was gathered through the parallel chart [33], i.e., a personal notebook, parallel to the clinical one, in which to write down thoughts and feelings in a plain language [34]. The patients

described in parallel charts could not coincide with patients participating in the project. Overall, these investigation tools (Supplementary file 2) addressed two common aspects: (a) the personal and social experience of RPE65-related IRDs from early symptoms onwards, and (b) the VRQoL perception and the current daily life with RPE65-related IRDs.

Furthermore, in-depth interviews [35] were conducted with MDT professionals and PA members to facilitate the emergence of patient-related issues further; the interviewees approved the transcripts before the analysis.

The investigation tools were designed by two ISTUD researchers with different academic backgrounds and reviewed by the Steering Committee to reduce any cognitive bias.

Patient and public involvement

Researchers did not engage patients and caregivers in (a) developing the research design and tools, (b) interpreting and discussing the results, and (c) contributing to the writing or editing of this document.

Ethical considerations

The project was performed according to the Declaration of Helsinki. Participants provided their web-based informed consent before their involvement and after being briefed on the project purposes and personal data processing procedures, according to the General Data Protection Regulation of the European Union 2016/679 [36] and the Italian Law 196/2003 [37]. Furthermore, the IRD specialists involved obtained a written informed consent from the parents of paediatric patients during the first briefing on the project methods and purposes.

The Ethical Committee of the Luigi Vanvitelli University Hospital (Naples, Italy) approved the project in September 2020 (protocol ID 20964/2020).

Analysis

Researchers analysed the sociodemographic data through descriptive statistics; answering survey questions or filling in fields in the illness plots and parallel charts was not mandatory, so sample size may vary. Narratives were entered into Nvivo software for coding and analysis [38]. Three narratives for each group and one in-depth interview were collectively coded to assess the consistency across team members; then, each narrative and in-depth interview were separately coded and reviewed during weekly peer debriefings to limit any interpretation bias.

Open interpretive coding was employed to identify and analyse the emerging topics in all narratives and in-depth interviews. Moreover, adult patients' and caregivers' narratives and parallel charts were classified following: (a) Kleinman's classification [23], which identifies *disease-*, *illness-*, and *sickness*-related aspects in narratives; (b) Bury's classification [39], which distinguishes among *contingent narratives* (concerning a condition's immediate effects on daily life), *core narratives* (connecting the illness experience to deeper and cultural levels of meaning) and *moral narratives* (highlighting an evaluative and social dimension).

Researchers asked the participants to describe RPE65-related IRDs through a metaphor to trace spontaneous meaning associations through daily language.

The Steering Committee discussed the results to address the emerged issues and data interpretation collectively. Researchers followed the Standards for Reporting Qualitative Research (SRQR) guidelines [40].

RESULTS

Three paediatric and five early-onset adult patients and eight caregivers participated in the project, as well as 11 retinologists specialised in IRDs, who wrote 27 parallel charts; all patients chose to share their experience in writing. In-depth interviews were conducted with five MDT professionals – i.e., two genetic counselors, two psychologists and one orientation and mobility (O&M) instructor

– and one PA member. Table 1 summarises the sociodemographic data of participants, including non-responders as a separate category.

Table 1 – Sociodemographic data of participants

	Patients (N=8)	Caregivers (N=8)	Patients in parallel charts (N=27)	Retinologists (N=11)	Professionals interviewed (N=6)
Gender					
Female	6 (75%)	6 (75%)	12 (44%)	5 (45%)	5 (83%)
Male	2 (25%)	2 (25%)	15 (56%)	6 (55%)	1 (17%)
Age (yrs)					
Median (range)	26 (8-63)	44 (31-70)	17 (5-65)	42 (32-64)	54 (49-67)
Geographic residence					
Northern Italy	3 (38%)	2 (24%)	-	-	2 (33%)
Central Italy	4 (50%)	4 (50%)	-	8 (73%)	4 (67%)
Southern Italy	1 (12%)	1 (13%)	-	3 (27%)	-
Non-responders	-	1 (13%)	-	-	-
Education					
Elementary school	1 (12%)	-	7 (26%)	-	-
Middle school	-	1 (12%)	4 (15%)	-	-
High school	1 (12%)	3 (38%)	4 (15%)	-	-
Bachelor/Master	3 (38%)	3 (38%)	3 (11%)	-	-
Non-responders	3 (38%)	1 (12%)	9 (33%)	-	-
Employment status					
Student	4 (50%)	-	16 (59%)	-	-
Working	3 (38%)	6 (76%)	10 (37%)	-	-
Not working	-	-	-	-	-
Retired	-	1 (12%)	1 (4%)	-	-
Non-responders	1 (12%)	1 (12%)	-	-	-
Marital state					
Single	6 (75%)	1 (12%)	18 (67%)	-	-
Married	2 (25%)	5 (64%)	7 (26%)	-	-
Separated	-	1 (12%)	2 (7%)	-	-
Non-responders	-	1 (12%)	-	-	-
Professional activity (yrs)					
Median (range)	-	-	-	16 (6-41)	23 (19-35)
Specialisation					
Ophthalmology	-	-	-	8 (73%)	1 (17%)
Paediatric ophthalmology	-	-	-	1 (9%)	
Orthoptics	-	-	-	2 (18%)	
Medical Genetics					1 (17%)
O&M Training					1 (17%)
Psychology					2 (32%)
Other	-				1 (17%)
Workplace					
Hospital	-	-	-	2 (18%)	

University Hospital	-	-	-	9 (82%)	2 (33%)
Other					4 (67%)

Data are presented as n(%) or median (range).

Results are presented along four main lines: (a) the RPE65-related IRDs experience analysed through narrative classifications and metaphors; (b) the emotional issues before and upon the clinical diagnosis; (c) VRQoL perception, the condition's impact on daily life and participants' expectations; (d) insights from in-depth interviews. Figures 1-3 and Tables 2-5 provide quotes from the narratives, while four narratives are available in English in Supplementary file 3; we reduced the risk of re-identification by applying different codes from those used to identify participants during data collection.

The RPE65-related IRDs experience in the narratives

Overall, almost all classified narratives highlighted illness-related aspects [23] (Figure 1); adult patients' narratives lacked a clinical language, which conversely characterised 63% of the caregivers' narratives and 37% of the parallel charts. Sickness-related issues were present in 50% of the caregivers' narratives and in 11% of the parallel charts, while they emerged in all adult patients' narratives.

[Figure 1]

Core narratives [39] prevailed in parallel charts (74%) and were equally reported (50%) as moral narratives by caregivers (Figure 2); only parallel charts presented contingent narratives (11%). Moral narratives were prevalent among adult patients (60%), while discomfort, disbelief (particularly at school) and the search for independence represented three spontaneously emerged issues in all narratives.

[Figure 2]

Metaphors were clustered into four thematic groups (Figure 3): (a) those referring to light and hope, used by patients (33%) and in parallel charts (15%); (b) those concerning limitations and impairment,

equally reported (50%) by patients and caregivers; (c) those related to darkness and mist, used by caregivers (33%) and in parallel charts (40%); (d) and metaphors denoting pain and isolation, almost equally used by patients and caregivers, and in parallel charts.

[Figure 3]

Emotional issues upon the clinical diagnosis and the clinical encounter

Patients reported having had the first signs of visual impairment at two years and three months of age (median value; range 0,5-6). In narratives, all patients reported issues that arose during early childhood, and that their parental caregivers identified as critical, e.g., being attracted by light sources or tripping (*In the evening, my parents used to cover the kitchen lamp, otherwise I would spend hours just staring at it*, Patient 002). As shown in Table 2, patients described early living with an RPE65-associated IRD either as uncomfortable (62%), mainly referring to the feeling of "being wrong", caused by the informal tests or eye examinations they were subjected to by their parents, or – conversely – normal (38%), since they did not have any standard of comparison to evaluate their sight. Caregivers reported having felt worried (50%) or helpless (50%) in the same years. During the communication of the clinical diagnosis, 71% of patients had no reaction, while the other 29% reported that it allowed them to identify their condition; conversely, parental caregivers (75%) felt hopeless, while partner caregivers (25%) reported concern for the hereditariness of the condition.

Table 2 – Patients' and caregivers' emotions before and at the diagnosis of RPE65-related IRD

		Patients
Before diagnosis	Normal (38%)	*– I have always felt normal. I never had the feeling that the slight differences I noticed could be a problem, or part of a problem*. (Patient 004)
	Uncomfortable (62%)	*– I felt their disappointment, their concern... They were not happy with me, and I felt wrong, because my answers were wrong. I couldn't see, and I couldn't help but guess...* (Patient 002)
At diagnosis	Identification (29%)	*– Somehow, finally identifying the problem brought me out of my limbo: for years, I had been the child who saw little during the day and who couldn't see at night; now I finally knew why. I became familiar with terms such as "blindness", "low vision", or "disability", concepts that would later radically change my future*. (Patient 001)

	Neutral (71%)	*– Honestly, I wasn't much affected. The disease has always been part of me. I grew up with it, I gradually got used to it*. (Patient 004)
	Caregivers	
Before diagnosis	Worry 50%	*– I felt helpless, terrified, and afraid*. (Caregiver 003)
	Helplessness 50%	*– I felt terrible, because I understood the challenge, but I couldn't do much, except hold her hand*. (Caregiver 006)
At diagnosis	Hopelessness 75%	*– I felt terrible. It's something you don't expect: a hereditary disease of a genetic nature in a family where there were no known cases seems impossible*. (Caregiver 008)
	Fear for children 25%	*– In the beginning, it scared me: the fear that our other children could suffer from a similar condition. Our anxiety decreased with time: I saw her, I saw she was restricted but not blocked, which gave me courage*. (Caregiver 005)

Table 3 summarises the clinicians' feelings the first time they met their patients and at the beginning of the care pathway. During the first visit, 37% of parallel charts reported the thought that the path would have been challenging, while 30% reported hopefulness over the care options; conversely, 22% focused on a sense of sorrow for the patient, and 11% on the empathy with patients or caregivers. At the beginning of the care relationship, clinicians felt on one side emotionally involved or motivated to do their best (58%), and on the other side helpless (30%) or "guilty" for being in a privileged situation compared to the patient (12%).

Table 3 – Retinologists' emotions at first visit and at the beginning of the care relationship

At the first visit	A challenge for both clinician and patient 37%	*– I thought that this visit was a challenge for us both: for her, it meant undergoing new tests and knowing the results; for me, it meant dedicating myself to another person to whom I could dedicate my care. I also thought that she might have access to treatment in the future, and I was ready and willing to facilitate this*. (Parallel chart 007)
	Hope 30%	*– I thought it was essential to follow her carefully from a clinical perspective, and that it was imperative to have a genetic test. When she showed it to me, I realized that she had a treatable mutation, which gave me hope*. (Parallel chart 015)
	Sorrow 22%	*– Poor child, he is not living his life like his healthy peers*. (Parallel chart 002)
	Empathy with patient or caregiver 11%	*– I thought that he was the same age as me, but that he had a completely different visual situation from mine. I stepped out of the treating doctor's shoes, and I found myself projected into an essentially human dimension. I put myself in her shoes and listened to her story with my heart as well as my ears*. (Parallel chart 006)
At the beginning of the care relationship	Emotional involvement and motivation 58%	*– I was impressed by what I was seeing, powerless but at the same time full of motivation and hope. I knew the child's mutation, and I imagined that – given his young age – he might have a therapeutic chance. I leveraged this last point in my talk with his parents, trying to give them a cautious hope and making them understand that this specific genetic*

	mutation meant being severely visually impaired, but also the possibility of being cured in a not distant future. (Parallel chart 005)
Helplessness 30%	*– Despite my knowledge, I felt powerless, unable to give immediate and concrete answers to many of his practical problems*. (Parallel chart 019)
Sense of guilt 12%	*– I felt ashamed... I'm lucky, I think I have a successful life, and yet I often get irritated or discouraged by stupid things, while he always seems happy to live his life, despite everything*. (Parallel chart 021)

In addition, 33% of the parallel charts highlighted the importance of showing empathy from the very beginning of the care relationship.

As for the currently living with an RPE65-related IRD (Table 4), patients reported a sense of uncertainty (25%), due to increasing visual impairment, or discomfort and sadness (25%); conversely, 50% reported to feel serene or hopeful, also considering the possibility of undergoing gene therapy. Caregivers declared to have accepted the condition (38%) and to live more serenely (62%), due to the awareness of having done their best. In parallel charts, clinicians reported positive feelings (44%), dedication (37%), and motivation (19%) toward patients.

Table 4 – The current feelings of participants: distribution and quotes from narratives

Patients	
Uncertainty 25%	*– Today I feel poised between light and shadow. I feel like someone who chases a ball without ever reaching it. I am 42 years old, and I have spent my life being told that science works miracles, and that life is long, and that progress for me will come soon. I am 42, though, not 10… My sight is progressively worsening. I feel tangible differences over a few months, days in some cases. I can remember things from a few months ago, visual details that I no longer see today. In fact, it's not that I don't see them: I perceive them as covered by a veil. Glossy... Like old photographs, but far less poetic...* (Patient 001)
Discomfort, sadness 25%	*– I feel sad: when mum or dad are driving, in the afternoon or in the evening, I do not see the road, I only notice a few lampposts*. (Patient 007)
Serenity, hope 50%	*– Today I feel hopeful for the future. I try every day to accept my challenges and to live with serenity. If the situation gets worse, I know that I will have to find different ways. It will be hard, maybe even unpleasant, but it will be possible. If the situation improves, thanks to gene therapy, I will be pleased*. (Patient 002)
Caregivers	
Acceptance 38%	*– I feel I am an integral part of my son's life. I live in symbiosis with him. Everything is more manageable: I manage to find solutions quite easily to meet his needs during his constant difficulties. Let's say that everything is always about having an obstacle to overcome... It's never easy, and sometimes it's mentally exhausting*. (Caregiver 003)
More serenity 62%	*– I know that we are doing our best to understand her condition better and, if possible, to start the therapy. The knowledge that we are doing our best brings me serenity*. (Caregiver 005)
Retinologists	

Positive feelings 44%	*—I'm feeling comfortable. Able to do my job without hiding my human side. Open to questions and ready to give competent and precise answers. Willing to help but aware of my limits, my role, and my possibilities*. (Parallel chart 006)
Commitment 37%	*—I feel obliged to give him what he hasn't had so far*. (Parallel chart 012)
Motivation 19%	*—I realize that it is a mutual gift. It reassures me to see her grow strong and able to face tomorrow despite her condition. I feel good with her, comforted by her positive attitude*. (Parallel chart 010)

VRQoL perception and daily living with RPE65-related IRDs

Supplementary file 4 presents survey data on patients' and caregivers' evaluation of RPE65-related IRDs impact on patients and their day-to-day tasks in relation to low light conditions; Figure 4 provides an overview of essential data.

[Figure 4]

Patients reported an increasing impact on main daily activities after sunset; thus, they referred both a severe impact on driving (100%) and cooking (100%), and no impact on the use of smartphones (86%) regardless of light conditions. Caregivers reported higher levels of limitation for patients in some activities even before sunset, such as reading, using digital tools or smartphones, washing, moving around; however, they reported fewer limitations in driving and cooking before sunset (100% *partially limited*). Considering an open coding of VRQoL domains in patient narratives, the limitation in activities was the prevalent issue, concerning 100% of patients' narratives. Mobility limitation (*–The city becomes more and more hostile. I am afraid of tripping, bumping into things, hurting myself, taking a wrong turn, being followed, and having to flee from a danger without being able to do so*, Patient 001), health concerns (*–I am sad and cry. I ask my mother if my eyes will ever be able to see well*, Patient 007) and emotional well-being issues (*–I cannot accept that I cannot do many things anymore, and I cannot admit that this leads me to close myself off*, Patient 006) emerged in 75% of patients' narratives.

Nevertheless, further survey data showed that 72% of patients considered their VRQoL good, and 14% excellent (Figure 5); thus, they reported that RPE65-related IRDs have enough impact on the

performance of their daily activities (83%). Fifty percent of caregivers defined their patient's VRQoL acceptable, and only 38% good; conversely, 30% and 14% reported that RPE65-related IRDs have a low – or no – impact on patients' performance of daily activities, respectively.

[Figure 5]

Addressing future perspectives, 71% of patients reported their hope to live serenely, both within their family and in the social context (*–I just want my loved ones to see me calm and serene. […] I could not bear to see my relatives feeling bad for me*, Patient 006), and 29% their hope to receive gene therapy (*–Thinking about tomorrow, I would like to receive gene therapy*, Patient 002); caregivers also stated to await gene therapy (50%). Clinicians hope to maintain a high quality of care in 41% of parallel charts, to improve their interpersonal skills and therapeutic possibilities for patients in 37%, and to be able to give them real hope in 22% (*–Sometimes I think that gene therapy has already become a reality, and I feel that I am living a surreal experience. […] I wish that what I perceive as surreal today soon becomes reality*, Parallel chart 007).

Overall, participants described writing as a positive experience: 27% of the caregivers' narratives and 21% of the parallel charts reported to consider it useful to raise awareness about these conditions; however, they also highlighted negative feelings, such as fatigue or sadness, in 14% and 8% of cases, respectively.

Insights from in-depth interviews

Five macro-themes transversely emerged from the in-depth interviews with MDT professionals and PA member (Table 5):

(a) The O&M instructor described the gap occurring between early-onset patients, who can develop compensatory strategies over time, and adult-onset patients, more likely to lose their previous visual experience. Thus, early-onset patients may experience their sight as "normal"; in this sense, the psychologists highlighted the importance to psychologically

support patients upon the communication of the clinical diagnosis, when introducing the notion of "impairment".

(b) According to all interviewees, psychological support should be provided throughout the care pathway to improve communication and avoid misleading messages that could make patients feel that they "could do nothing more". Furthermore, as also maintained by the genetic counselors and the PA member, a more careful communication would allow the patient to keep an active perspective on the care pathway and early address rehabilitation programs.

(c) All interviewees addressed the RPE65-related IRDs impact on parental and partner caregivers. While the latter may face a couple crisis due to the progression of the impairment, the former often deal with the failure of the "perfect child" dream, the hope that they children will heal and a strong sense of guilt for the inheritability of the condition. Since caregivers project these complex feelings on patients, potentially impacting their care pathway, a psychological support should be provided to help them accept this condition.

(d) All interviewees highlighted the lack of knowledge of IRDs among the general public and society. The O&M instructor stressed that the link between visual impairment and changing light conditions is challenging for those who do not know these diseases. The psychologists confirmed that this is also critical in the school environment. One psychologist and the PA member mentioned the need to create an IRDs "culture" and to address the diversity issue.

(e) Furthermore, one psychologist focused on the need for investigation tools integrating quantitative questionnaires to address the interpersonal dimension of daily activities, especially after sunset or in low light conditions.

Table 5 – Macro-themes reported by MT professionals and PA representative interviewed: quotes from in-depth interviews

Managing IRDs	*– In some people, the degenerative process begins during adulthood. They "unconsciously" erase all their previous visual experiences: it's a psychological reaction to the condition. Thus, they really need a "carer" because they can no longer do anything.*

	Their mind forgets and cannot retrieve all the skills they possessed before from their store of experiences. On the other hand, in children who are used to this type of vision from an early age, visual function adapts, even if it gradually diminishes. They can create compensatory strategies more quickly, even if, while working on it, we realize that their visual acuity or visual field have worsened. (Interviewee 002)
Communication of the diagnosis	– *[...] Colleagues who are not familiar with this condition are sometimes caught off guard. In the past, there have been communication issues. [...] Over the years, I have seen everything: from diagnoses not being communicated even when clear and evident, to children being told to learn Braille. Sometimes prognoses were communicated incorrectly; patients perceived them as crude, or they were told not to have children, because they would all be suffering from the same condition.* (Interviewee 001) – *We still have situations where the diagnosis is communicated violently: unfortunately, there is no cure for the disease, blindness could occur, but we do not know when... Verbal violence is where any kind of hope is taken away. [...] The main issue after the diagnosis is the psychological one. Suppose the diagnosis is communicated together with the possibility of recuperation, in which case one can deal with it somehow; but if it is expressed without this possibility, people don't even undergo check-ups anymore*. (Interviewee 004)
Attention to partner and parental caregivers	– *Some couples, [...] when they discovered the condition experienced a crisis. [...] What I noticed is that the way a caregiver treats his/her partner changes a lot: It's more imperative* (Interviewee 002) – *A parent cannot serenely accept the condition of a child. Mothers are confronted with this issue daily, i.e., they are considered "good mothers" if they can accept it, and this translates into the thought "I am not a good mother, I will not be a good mother". [...] These parents often call the child "sick". Disability is not a disease, but a condition. In pregnancy, parents expect to have a "healthy" child: the hope is to regain this healthy child, even when it is objectively impossible.* (Interviewee 003)
Lack of knowledge of IRDs	– *In terms of daily life, people with this condition experience uncertainty, which is not even daily, but hourly. They may not see the same things at 10:00 and 10:30 am, because of a series of parameters that come into play: size, permanence, brightness, which give the retina a different visual function. So, this uncertainty generates other insecurities, and often triggers profound depressive states. This is not understood by other people. Often, at school, teachers do not understand how the child could see the blackboard at the beginning of the lesson and not at the end. The explanation is evident to those who know these disorders: maybe the sun's angle had changed, of fatigue may come in to play, together with a series of parameters that determine a visual loss*. (Interviewee 002) – *I believe that initiatives are needed to allow people gain experience. For children, we could think of initiatives in school, which should be carried out regardless of the presence in the class of a child with this condition. We need to create a "culture" [...], a culture of confrontation with diversity*. (Interviewee 003)
New investigation tools	– *The dimension of being with others is entirely missing: all activities are investigated as if they were carried out by the person alone, but rarely people with this condition are alone, especially after sunset*. (Interviewee 003)

DISCUSSION

The project represents the first effort to investigate RPE65-related IRDs in Italy through NM, simultaneously addressing the perspectives of patients, caregivers and treating retinologists and collecting insights from MDT professionals and PA members.

The co-presence of *illness*- and *sickness*-related aspects [23] and the lack of a clinical language in patient narratives highlighted the centrality of the personal and social dimensions of living with an RPE65-related IRD in narrating the illness experience and trying to make sense [10] of the condition; the prevalence of moral narratives [39] supports this suggestion. The employed classifications allowed related themes to emerge in narratives spontaneously: patients declared to have manifested the first signs of visual impairment during early childhood and reported a discomfort mainly due to the informal testing they were subjected to by their parents, together with repeated eye examinations, before the clinical diagnosis; at school, their visual impairment is misunderstood or questioned by their teachers, who are not aware of the relationship between visual impairment and changing light conditions. In-depth interviews confirm the lack of knowledge about IRDs among the general public and society, as well as at school, where patients also experience stigma [41] since their visual issues are addressed like cognitive impairments. Further investigations on the school environment may integrate studies on the patients' discrimination at their workplace [42] and studies on the patients' feeling of being often patronised [10].

Early-onset patients perceive their sight as "normal", finding out to be "impaired" only after the clinical diagnosis or by interacting with their peers in the school environment. As emerged from the in-depth interviews, the notion of "impairment" should be carefully introduced to support the patients' awareness of their condition. This issue may be further explored and integrated with studies on making sense and coping with IRDs [10, 12], while careful communication should be adopted throughout the care pathways.

The search for autonomy emerges as related to the health concerns for the progressive sight loss and the emotional well-being issues showing anxiety for the future. Findings confirm that RPE65-related IRDs significantly impact patients' VRQoL in terms of activity and mobility limitations: while changing light conditions do not change the use of digital tools or smartphones, activities such as

driving and cooking remain challenging, regardless of the light conditions; moreover, the capability to perform daily activities is compromised by low light conditions, as also shown in studies addressing IRD critical effects on lifestyle choices [11, 43]. Nonetheless, many patients reported having a good VRQoL, suggesting that they have found strategies to cope with the condition in the absence, so far, of a therapeutic solution; these coping strategies should be further investigated. Also, two considerations may be emphasised: on the one side, the narratives and survey data show misalignment between the patient's and the caregiver's perception of the former's limitation in activities and in VRQoL, where patients report a higher perceived VRQoL, and conversely a lower performance while carrying out daily tasks. On the other side, the search for autonomy is linked with the perception that relying on others is a limitation, confirming previous studies on this topic [11].

The metaphors used by patients to describe RPE65-related IRDs highlight not only limitations and pain, but also lights and hope. Conversely, the association with images recalling darkness emerges from caregiver narratives and parallel charts; in particular, caregivers do not use any positive image to describe RPE65-related IRDs.

In contrast with patients, caregiver narratives largely focus on *disease*-related aspects [23]; however, the presence of *sickness*- and *illness*-related aspects suggests their emotional commitment to the patient's well-being. Furthermore, moral narratives [39] reveal the sense of guilt experienced by caregivers about the hereditariness of the condition, which is also addressed within in-depth interviews: while partner caregivers may face a couple crisis upon the onset of the condition, parental caregivers experience the failure of the "perfect child" dream and struggle to accept the condition. Misalignment in the patients' perception of their VRQoL, metaphors, and the emotional issues reported also suggest the complexity found by caregivers in coping with these conditions.

Parallel charts show that retinologists are personally and emotionally involved in the care relationship, as suggested by the prevalence of core narratives [39] and reported their feelings at the beginning of the care pathway, despite being less focused on social RPE65-related IRDs aspects. Retinologists emerge as being motivated to find the most suitable therapeutic pathway, as well as emotionally committed to patients; for the first time in similar NM projects, clinicians report a clear sense of guilt for being "healthy" compared to their patients.

These are only preliminary findings; however, they can provide initial insights on the importance of a multidisciplinary RPE65-related IRDs clinical practice:

(a) RPE65-related IRDs critically impact several quality-of-life domains, while the emotional aspects of RPE65-related IRDs emerge as crucial while making sense of the condition and during the clinical encounter: the tension between the individual and the social dimensions of these conditions emerged as informative of the care pathway challenges and real-life experiences, and may be better addressed through new investigation tools, as claimed by the in-depth interviews. The NM approach has proved to be suitable for this purpose.

(b) The emotional burden of caregiving remains poorly investigated. Nonetheless, narratives show that caregivers deeply participate in the patient's illness experience, while the in-depth interviews recommend a psychological support to help them accept the condition, while potentially improving the care pathway.

(c) The need for an RPE65-related IRDs "culture" emerges as crucial to acknowledge these conditions, to avoid perpetuating the stigma and the scepticism and to foster the debate on diversity at society level.

Since narratives were anonymous, we are not able to precisely state the misalignment between patients and caregivers regarding the performance of daily activities and the perception of VRQoL. Further investigations are needed to examine in more details the issues which spontaneously

emerged, also involving the work sphere. The annual incidence of RPE65-related IRDs explains the low number of participating patients [44]; however, the narratives collected suggest a strong dedication to the project and a relationship of trust between patients, caregivers and the retinologists from the centres involved. Finally, the data collection phase partially coincided with the local measures decided by the Italian government to contain the Sars-Cov-2 pandemic, with consequences on the clinical follow-up and the participation in the project.

CONCLUSION

The project investigated the practical and emotional issues of RPE65-related IRDs as experienced by patients, caregivers, and retinologists, and provided insights from MDT professionals and PA members. It represented the first Italian project that simultaneously addresses and integrates these perspectives, whose comparison allowed to provide preliminary suggestions useful for the clinical practice and the knowledge of RPE65-related IRDs. NM allowed to connect the impact of RPE65-related IRDs on quality-of-life domains with real-life experiences, emerging as informative in raising suggestions to improve the care pathway for these conditions.

Abbreviations

IRDs – Inherited Retinal Disorders

RPE65 – Retinal pigment epithelium-specific 65 kDa protein

LCA – Leber congenital amaurosis

RP – Retinitis Pigmentosa

VRQoL – Vision-Related Quality of Life

WHO – World Health Organization

NM – Narrative Medicine

MDTs – Multidisciplinary teams

PA – Patient Association

WCAG – Web Content Accessibility Guidelines

SRQR – Standards for Reporting Qualitative Research

DECLARATIONS

Ethics approval

The project was conducted according to the Declaration of Helsinki. The Ethical Committee of the Luigi Vanvitelli University Hospital (Naples, Italy) approved the project rationale, design, investigation questionnaires and informed consent in September 2020 (protocol ID 20964/2020).

Consent to participate

Participants provided a web-based informed consent before their involvement and after being briefed on the purposes of the research and the procedures for the processing of personal data, according to General Data Protection Regulation of the European Union 2016/679 and the Italian Law 196/2003. The clinicians involved obtained a written informed consent to participate from the parents of underage patients during the first briefing on the project's methods and purposes.

Consent for publication

Not applicable.

Data sharing

All datasets used and analyzed during the current research are available in Italian from the corresponding author, upon reasonable request.

Competing interests

MA and NF are employees of Novartis Pharmaceuticals, Italy, and Region Europe. FS, BF, GB, and GI have received honoraria from Novartis Pharmaceuticals, Italy, for holding webinars. FS, AS, IP, IDR have received honoraria from Novartis Pharmaceuticals, Italy, for serving on advisory boards.

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Authors' contributions

FS, AS, BF, GB, GI, AA, LR, NF and MA were involved in the project's conceptualization. MGM, LR, and AF were involved in the methodology. FS, AS, BF, GB, GI, VDI, DG, GP, AA, GBV, AC, SDS, IDR, SF, CM, DPM, VM, IP and ST contributed to the project's investigation. RL and MA were involved in the project's administration. LR and AF contributed to data analysis. FS, AS, BF, GI, VDI, DG, GP, AA, LR and MA contributed to data validation. AF, LR and MA were involved in writing; all authors contributed to the manuscript review and read and approved the final draft for submission.

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References

1. Broadgate S, Yu J, Downes SM, Halford S. Unravelling the genetics of inherited retinal dystrophies: Past, present and future. *Progress in Retinal and Eye Research*. 2017; 59.
2. Ziccardi L, Cordeddu V, Gaddini L, Matteucci A, Parravano M, Malchiodi-Albedi F, et al. Gene therapy in Retinal Dystrophies. *In J Mol Sci*. 2019 Nov 14; 20(22).
3. Kang C, Scoo LJ. Voretigene Neparvovec: A Review in RPE65 Mutation-Associated Inherited Retinal Dystrophy. *Mol Diagn Ther*. 2020 Aug; 24(4).
4. Duncan JL, Pierce A, Laster AM, Daiger SP, Birch DG, Ash JD, et al. Inherited retinal degenerations: Current landscape and knowledge gaps. *Transl Vis Sci Technol*. 2018;7.
5. Tsang SH, Sharma T. Leber Congenital Amaurosis. *Adv Exp Med Biol*. 2018; 1085.
6. Tsang SH, Sharma T. Retinitis Pigmentosa (Non-syndromic). *Adv Exp Med Biol*. 2018; 1085.

7. Jacobson SG, Aleman Ts, Cideciyan AV, Roman AJ, Sumaroka A, Windsor EA, et al. Defining the residual vision in Leber congenital amaurosis caused by RPE65 mutations. Invest Ophthalmol Vis Sci. 2009 May; 50(5).
8. Russell S, Bennet J, Wellman JA, Chung DC, Yu ZF, Tillman A, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet. 2017 Aug 26;390(10097).
9. Thompson DA, Ali RR, Banin E, Branham KE, Flannery JG, Gamm DM, et al. Advancing therapeutic strategies for inherited retinal degeneration: recommendations from the Monaciano Symposium. *Invest Ophthalmol Vis Sci*. 2015;56(2).
10. Thurston M, Thurston A, McLeod J. Socio-emotional effects of the transition from sight to blindness. *British Journal of Visual Impairment*. 2010; 28(2).
11. Prem Senthil MP, Khadka J, Pesudovs K. Seeing through their eyes: lived experiences of people with retinitis pigmentosa. Eye. 2017;31(5).
12. Bittner AK, Edwards L, George M. Coping strategies to manage stress related to vision loss and fluctuations in retinitis pigmentosa. Optometry. 2010; 81(9).
13. Lloyd A, Piglowska N, Ciulla T, Pitluck S, Johnson S, Buessing M, et al. Estimation of impact of RPE65-mediated inherited retinal disease on quality of life and the potential benefits of gene therapy. *Br J Ophthalmol*. 2019 Nov;103(11).
14. Chacón-López H, Pelayo FJ, López-Justicia MD, Morillas CA, Urena R, Chacon-Medina A, Pino B. Visual training and emotional state of people with retinitis pigmentosa. J Rehabil Res Dev. 2013;50.
15. Kempen GI, Ranchor AV, Ambergen T, Zijlstra GR. The mediating role of disability and social support in the association between low vision and depressive symptoms in older adults. *Qual Life Res*. 2014; 23(3).
16. Parmeggiani F, Sato G, De Nadai K, Romano MR, Binotto A, Costagliola C. Clinical and Rehabilitative Management of Retinitis Pigmentosa: Up-to-Date. *Curr Genomics*. 2011 Jun;12(4).
17. Garip G, Kamal A. Systematic review and meta-synthesis of coping with retinitis pigmentosa: implications for improving quality of life. *BMC Ophthalmology* (2019) 19.
18. Pierret J. The illness experience: state of knowledge and perspectives for research. *Sociol Health Illn*. 2003; 25.

19. Greenhalgh T. Cultural contexts of health: the use of narrative research in the health sector. Copenhagen: WHO Regional Office for Europe; 2016, Health Evidence Network (HEN) synthesis report 49. http://www.euro.who.int/__data/assets/pdf_file/0004/317623/HEN-synthesis-report-49.pdf, last accessed on March 23, 2021.
20. Nowaczyk MJ. Narrative medicine in clinical genetics practice. Am J Med Genet A. 2012 Aug;158A(8).
21. Ragusa L, Crinò A, Grugni G, Reale L, Fiorencis A, Licenziati MR. Caring and living with Prader-Willi syndrome in Italy: integrating children, adults and parents' experiences through a multicenter narrative medicine research. BMJ Open 2020;10.
22. Marini MG. Narrative Medicine: Bridging the Gap between Evidence-based Care and Medical Humanities. London: Springer International Publishing 2016.
23. Kleinman A. The Illness Narrative, Suffering and Healing the Human Condition. New York: Basic Book 1989.
24. Greenhalgh T, Hurwitz B. Why study narrative? *BMJ* 1999; 318.
25. Marini MG, Languages of Care in Narrative Medicine. Words, Space and Time in the Healthcare Ecosystem. London: Springer International Publishing 2019.
26. Fioretti C, Mazzocco K, Riva S, Oliveri S, Masiero M, Pravettoni G. Research studies on patients' illness experience using the Narrative Medicine approach: a systematic review. *BMJ Open* 2016; 6.
27. Simonelli F, Sodi A, Falsini B, et al. Care pathway of RPE65-related inherited retinal disorders from early symptoms to genetic counseling: a multicenter Narrative Medicine project in Italy. *Clinical Ophthalmology*. In Press, 2021.
28. Audo I, Williamson N, Bradley H, Barclay M, Sims J, Arbuckle R, et al. Qualitative exploration of patient and caregiver experiences of visual function impairments and impacts on vision-dependent activities of daily living and health-related quality of life associated with Retinitis Pigmentosa and Leber Congenital Amaurosis in Germany and France. *Invest. Ophthalmol. Vis. Sci.* 2021;62(8):3585.
29. Kay C, Williamson N, Bradley H, Barclay M, Sims J, Arbuckle R, et al. Qualitative interviews with patients and caregivers regarding visual function impairments and impacts on vision-dependent activities of daily living and health-related quality of life in RPE65-related Retinitis Pigmentosa and Leber Congenital Amaurosis. *Invest. Ophthalmol. Vis. Sci.* 2021;62(8):3589.

30. Web Content Accessibility Guidelines (WCAG) 2.1. W3C Recommendations 05 June 2018. Available at https://www.w3.org/TR/WCAG21/, last accessed March 23, 2021.
31. Reid K, Soundy A. A qualitative study examining the illness narrative master plots of people with head and neck cancer. *Behav Sci* 2019; 9.
32. Peeters B, Marini M. Narrative medicine across languages and cultures: using minimal English for increased comparability of patients' narratives. In: Goddard C, ed. Minimal English for a Global World: Improved Communication Using Fewer Words. Basingstoke, UK: Palgrave Macmillan 2018: 259–86.
33. Charon R. The patient-physician relationship. Narrative Medicine: a model for empathy, reflection, profession, and trust. *JAMA* 2001; 286.
34. Banfi P, Cappuccio A, Latella ME, et al. Narrative medicine to improve the management and quality of life of patients with COPD: the first experience applying parallel chart in Italy. *Int J Chron Obstruct Pulmon Dis* 2018; 13.
35. Brédart A, Marrel A, Abetz-Webb L, Lasch K, Acquadro C. Interviewing to develop Patient-Reported Outcome (PRO) measures for clinical research: eliciting patients' experience. *Health Qual Life Outcomes*. 2014 Feb 5.
36. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation. Published on the Official Journal of the European Union L 119, May 4, 2016. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679, last accessed on March 23, 2021.
37. Personal data code protection. Legislat. Decree no. 196 of 30 June 2003. Published on the Italian Official Journal n. 174, July 29, 2003, Supplementary n. 123. https://www.camera.it/parlam/leggi/deleghe/Testi/03196dl.htm, last accessed on March 23, 2021.
38. Bazeley P, Jackson K. Qualitative Data Analysis with NVivo. London: SAGE 2013.
39. Bury M. Illness narratives: fact or fiction? Sociology of Health and Illness. 2001;23(3).
40. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care*. 2007 Dec;19(6).
41. Goffman E. Stigma. London: Penguin, 1963.

42. Spiegel T, De Bel V, Steverink N. Keeping up appearances: the role of identity concealment in the workplace among adults with degenerative eye conditions and its relationship with wellbeing and career outcomes. Disabil Rehabil. 2016;38(7)

43. Prem Senthil M, Khadka J, Gilhotra JS, Simon S, Pesudovs K. Exploring the quality of life issues in people with retinal diseases: a qualitative study. J Patient Rep Outcomes. 2017;1(1).

44. Lorenz B, Tavares J, van den Born LI, Marques JP, Scholl HPN; EVICR.net Group. Current management of patients with RPE65 mutation-associated inherited retinal degenerations (IRDs) in Europe. Results of a multinational survey by the European Vision Institute Clinical Research Network EVICR.net. *Ophthalmic Res*. 2021 Mar 8.

Figure legend

Figure 1 – Kleinman's classification: distribution and quotes from narratives.

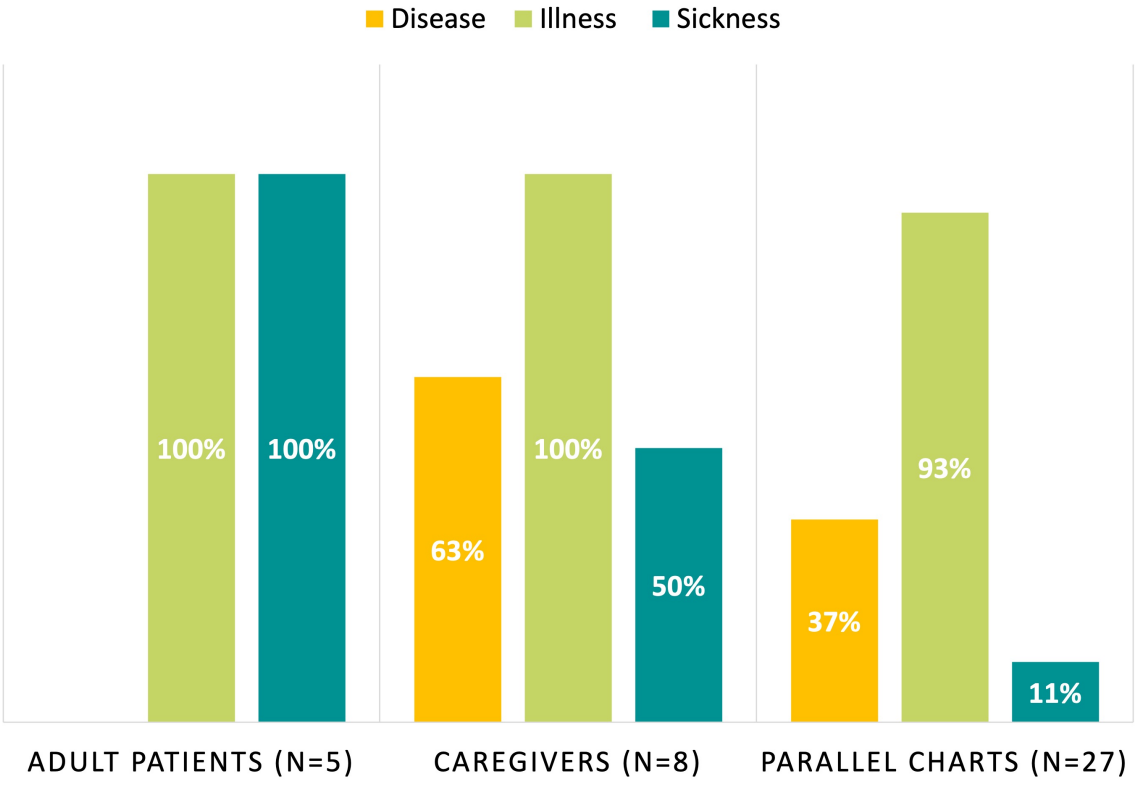
Figure 2 – Bury's classification: distribution and quotes from narratives.

Figure 3 – Metaphors used to describe RPE65-related IRDs: distribution and examples.

Figure 4 – Reported limitations in activities by patients and caregivers: essential data.

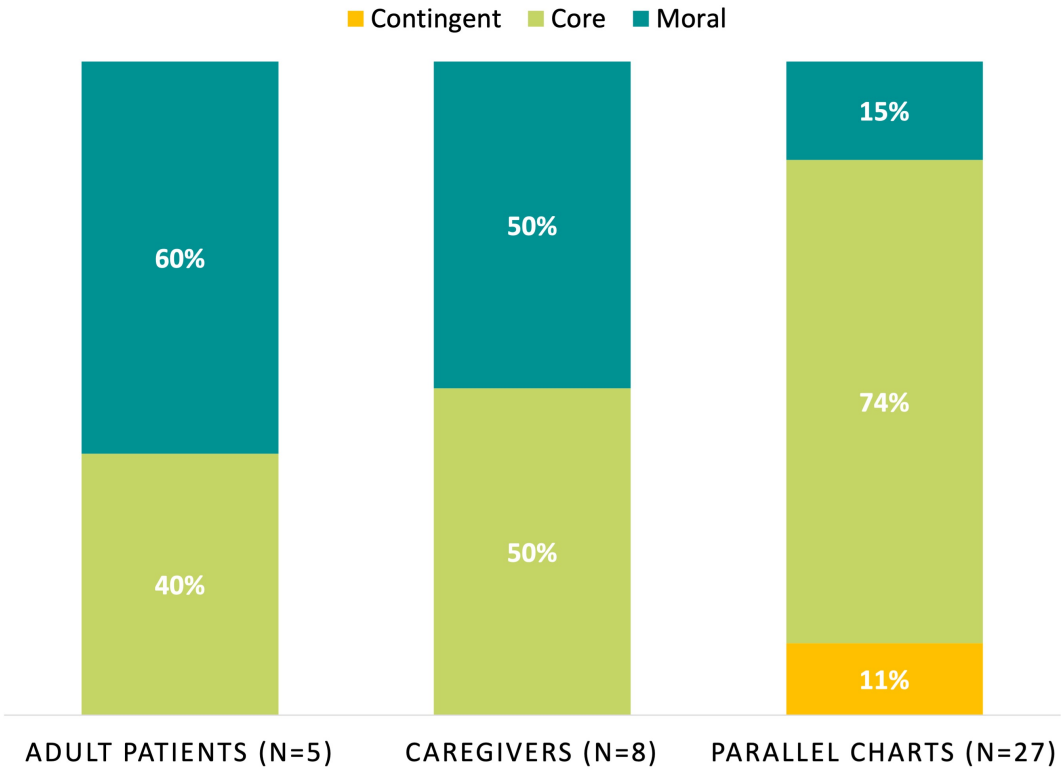
Figure 5 – Patients' QoL and RPE65-related IRDs overall interference on activities as perceived by patients and caregivers.

Figure 1 — Kleinman's classification: distribution and quotes from narratives



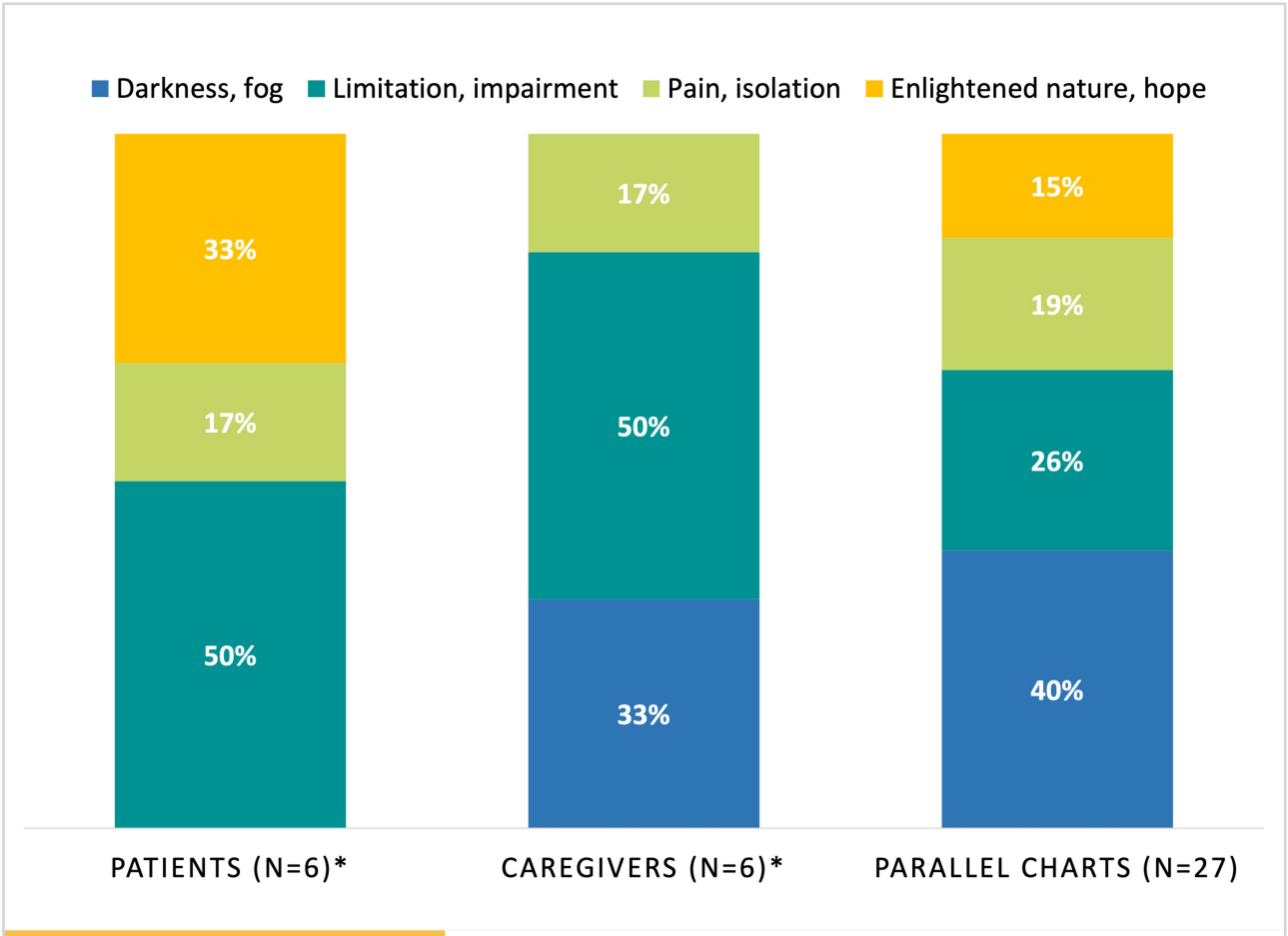
Disease	*—[...] All our research concentrated on what we observed, on the symptoms shown by our little girl: hyper fixation of light sources (light gazing), pressure on the eye sockets with the fingers (Franceschetti's oculo-digital sign), strabismus, failure to follow faces and objects, erratic movements of the pupils (nystagmus) and hypermetropia, which in ophthalmological medical literature led to a specific pathology*. (Caregiver 004) *—I thought he had Leber congenital amaurosis because of the head attitude and Franceschetti's oculo-digital sign together with nystagmus*. (Parallel chart 011)
Illness	*—I feel powerless because I cannot stop the progress of this disease. But at the same time, I feel serene because I have all the tools I need to cope with what will come. I feel melancholic because I know I will never again be able to do what I am doing today or what I did yesterday*. (Patient 004) *—When I was told it was an RPE65-related IRD, I felt empty inside, unable to realise the situation; I had never even heard of this condition*. (Caregiver 003) *—The child could not do many things and was fragile. I empathised with her parents' pain*. (Parallel chart 003)
Sickness	*—One afternoon, I was walking home with a friend and a classmate. We were chatting quietly when suddenly this boy introduced me to his grandmother as "the blind girl"*. (Patient 005) *—It was complicated to relate to other people and to make them understand the condition*. (Caregiver 006) *—Relationships with others are complex: relatives and friends instinctively protect these patients for fear that they might harm themselves*. (Parallel chart 019)

Figure 2 — Bury's classification: distribution and quotes from narratives



Contingent	*—I suspected the presence of retinal dystrophy. I went through the process of confirming my diagnostic suspicion*. (Parallel chart 009)
Core	*—Everything was unlocked when I realised that it was not difficult to ask for and accept help from others; that it wasn't so difficult to be different. Seeing – or rather, not seeing – was challenging to explain to others as long as it was difficult for me to accept*. (Patient 002) *—Today I feel calm. I have learned to accept this problem. I see that she gets by somehow; I always hope it doesn't get worse. I hope she has the opportunity to be treated because then she could be self-sufficient in doing things. I see her happy and hopeful*. (Caregiver 001) *—All patients always teach us something: paediatric patients often make us understand aspects of the disease that do not emerge with adults*. (Parallel chart 020)
Moral	*—Others say, judge, pity... Others are as unprepared for visual impairment as we are for death. The others are a disaster... A disaster to be reckoned with*. (Patient 001) *—I was angry, confused, incredulous. It's not fair. Why her? Why us?* (Caregiver 007) *—Sometimes I felt almost guilty for having healthy children. I looked at the parents – my peers – and saw their despair*. (Parallel chart 008)

Figure 3 - Metaphors used to describe RPE65-related IRDs: distribution and examples



Enlightened nature, hope	*—The world to me is a beautiful impressionist painting: as fascinating as it is imprecise... Shaded and inexact brushstrokes of colour... A world more imagined than seen, and yet, I would want to miss this painting for nothing in the world*. (Patient 001) *—A sun hidden in the clouds*. (Parallel chart 018)
Darkness, fog	*—This condition is like a thick, ever-present fog... it takes away your light, colours, and tiny details*. (Caregiver 005) *—A dark veil is dropped in front of his eyes and does not allow him to see the world as it should be seen but through a barrier*. (Parallel chart 005)
Limitation, impairment	*—Having this disease is like being a bird with only one wing. You only fly with the help of someone else*. (Patient 002) *—A horse with blinkers that cannot see to the sides*. (Caregiver 002) *—A bird in a cage*. (Parallel chart 025)
Pain, isolation	*—An eye with a monster eating it*. (Patient 005) *—A tear that runs down my child's face from her eyes; it runs long and doesn't stop...* (Caregiver 007) *—A child playing alone*. (Parallel chart 016)

*Non-responses = 2

Figure 4 - Reported limitations in activities by patients and caregivers: essential data

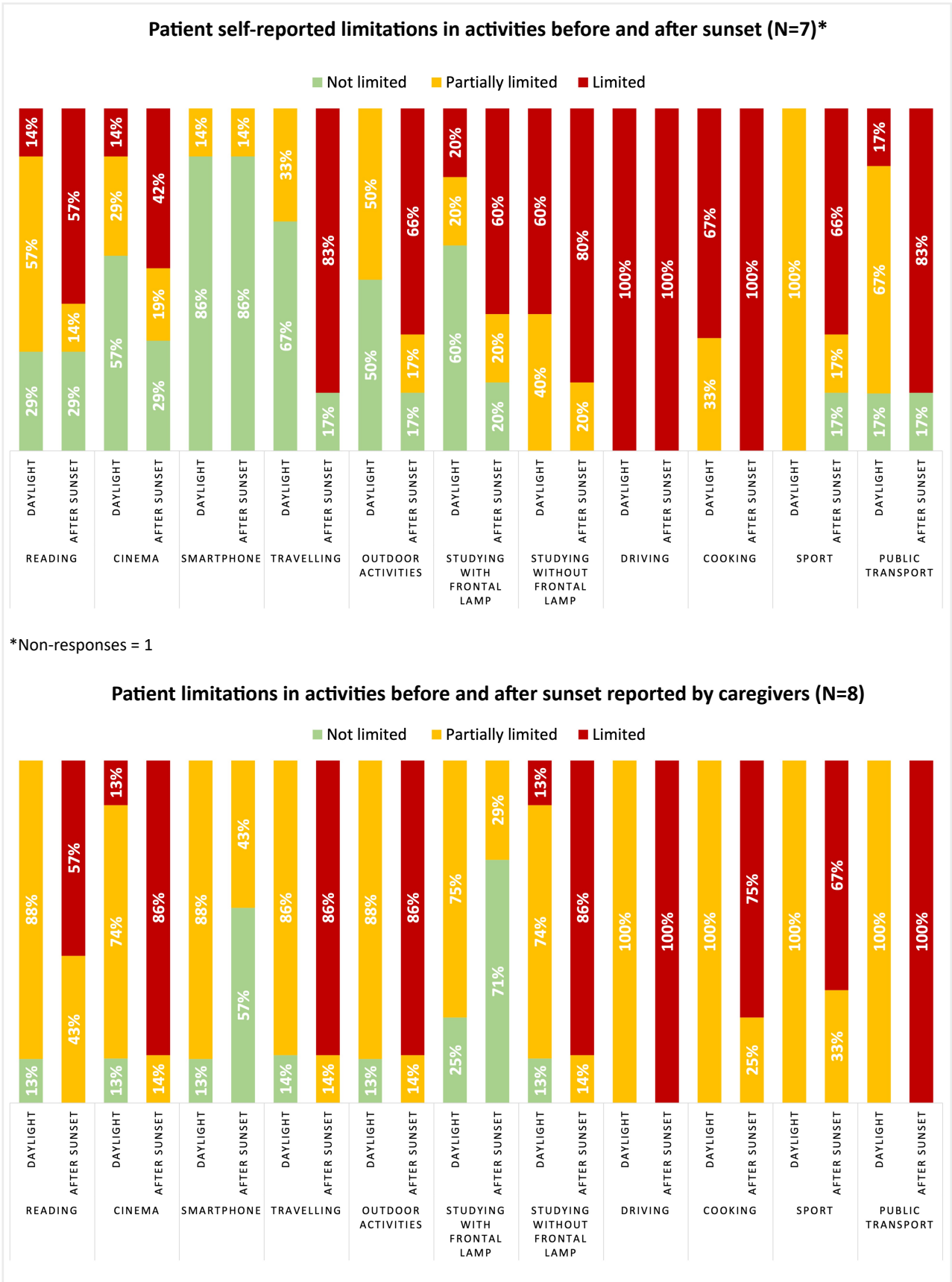
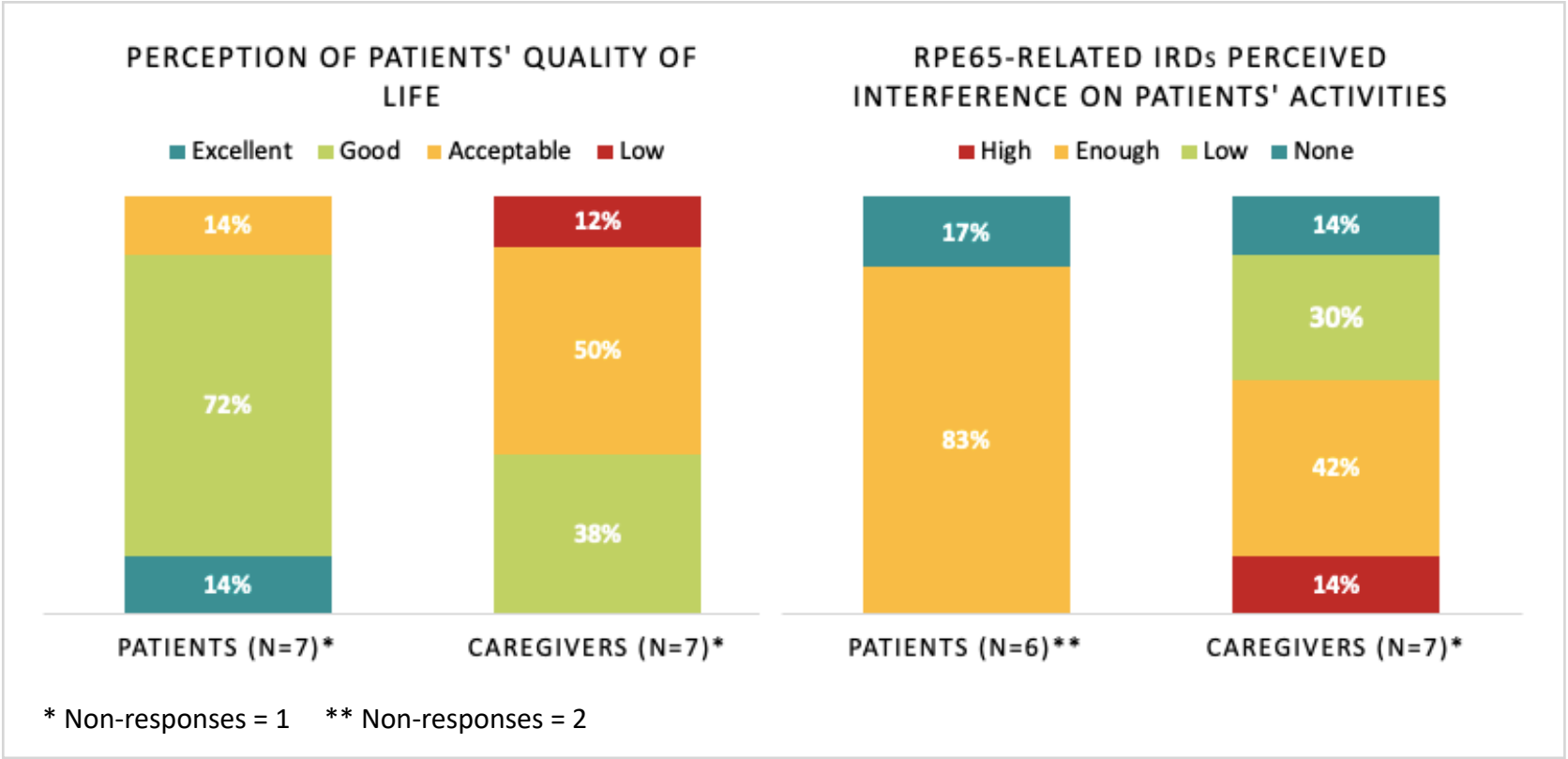


Figure 5 - Patients' QoL and RPE65-related IRDs overall interference on activities as perceived by patients and caregivers



* Non-responses = 1 ** Non-responses = 2

Supplementary file 1

Eye clinics specialised in Inherited Retinal Disorders (IRDs) involved in the BIRDS project

1. CRR Hereditary Retinal Degeneration, Careggi University Hospital – Florence, Italy
2. Paediatric Ophthalmology Unit, Children's Hospital A. Meyer – Florence, Italy
3. Department of Ophthalmology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore – Rome, Italy
4. Ophthalmology Department, Bambino Gesù IRCCS Paediatric Hospital – Rome, Italy
5. Multidisciplinary Department of Medical Surgical and Dental Specialties, Luigi Vanvitelli University Hospital – Naples, Italy

Supplementary file 2 – Illness plots and parallel chart

2.1. Illness plot addressed to patients

We invite you to tell us about your experience of living with a hereditary retinal disorder related to the RPE65 gene (RPE65-related IRD). You can write instinctively and freely, regardless of the form and length of your narrative. Any episode you consider significant will be welcome.

Before the IRD clinical diagnosis… The first signs that something was wrong… I felt… To understand what it was about… The facilities I visited, the healthcare professionals I met… Waiting for the clinical diagnosis… When they told me that it was an IRD, I felt... The genetic test for me was... That time, with family... With others... For me, seeing was... The activities I liked to do... The activities I could not do... At school/work... Healthcare professionals and treatments were... The centre where I am treated… Healthcare professionals and treatments are… Gene therapy for me is… Between one visit and the next… With my family… With other people… For me, seeing is… The activities I like to do… The activities I cannot do… Today at school/work… Rethinking about my care pathway, I would have liked that… Thinking about tomorrow, I feel… For tomorrow, I would like to…

Thank you for your time, energy and attention. We ask you one last question: How did you feel about writing your experience?

2.2. Illness plot addressed to caregivers of patients with an RPE65-related IRD

We invite you to tell us about your experience of living next to a person with a hereditary retinal disorder related to the RPE65 gene (RPE65-related IRD). You can write instinctively and freely, regardless of the form and length of your narrative. Any episode you consider significant will be welcome.

Before the diagnosis of IRD... When we first noticed that something was wrong... I felt... She/he felt... To find out what it was... Looking at her/him I thought... The facilities we visited, the healthcare professionals we met... Before the IRD clinical diagnosis... When we were told that it was an IRD, I felt... For me, the genetic test was... At that time, she/he with the family... She/he with other people... For her/him, seeing was... The activities she/he liked to do... The activities she/he could not do... At school/work... For her/him, I wanted... Healthcare professionals and treatments were... Today I feel... Today she/he feels... The IRD is... The centre where she/he is treated... Treatments and caregivers are... Gene therapy for me is... Between one visit and the next… With family... With other people… For her/him, seeing is... The activities she/he likes to do... The activities she/he cannot do... Rethinking to the care pathway, I would have liked that... Thinking about tomorrow, I feel... For tomorrow, I would like to...

Thank you for your time, energy and attention. We ask you one last question: How did you feel about writing your experience?

2.3. Parallel chart on patients affected by an RPE65-related IRD addressed to healthcare professionals

The first time I saw this person with an IRD, I thought… The patient and her/his relatives told me... Addressing symptoms, they told me that she/he could do/not do... I felt… And I did... Waiting for the clinical diagnosis... When I had to communicate the clinical diagnosis... Proposing the genetic test was... The relationships with family and other people of the person with IRD… For her/him, seeing was... Between one visit and the next… In her/his activities at work/study/play... Today this person... With family and other people... Today this person, during work/study/play… The people next to her/him... My goal for this patient is... With her/him I feel... From the relationship with the patient, I've learned... For tomorrow, I wish that I… For tomorrow I hope she/he...

Thank you for your time, energy and attention. We ask you one last question: How did you feel about writing your experience?

Supplementary file 3

3.1. Narrative from an underaged patient affected by an RPE65-related IRD

My mum realised that something was wrong when I was very young, about 18 months. I never felt different and was unaware of the difficulties. The professionals I met were helpful, kind, welcoming people who made me feel at home. While waiting for the diagnosis, I was very calm. When they told me that it was a hereditary retinal disease, nothing had changed for me. My eyes did not work as well as a healthy child's. The genetic test was a big step for me. The genetic test was just another test for me. At that time, we were very relaxed in my family. We had no particular problems with others. I've always seen that way. I don't know how others see. I like skating, dancing and cycling. At first, I could not ride a bike, then I did. I like school a lot, so I do not have any difficulties.
Some pills I will remember all my life because they were terrible, but the rest of the treatment was easy. Today I feel happy. The disease is stable for now, and I feel calm. I have more than one centre, and they are doing everything they can. The doctors are very nice and friendly, and I don't have any special treatment. Gene therapy is a great possibility for me because it will help keep my eyes stable, which would be very positive. Between one visit and the next, I feel calm and have no particular tension. I feel very relaxed with my family. With others, I am a sunny child. Seeing is a beautiful thing because it allows me to relate to the outside world. I like riding my bike, being with my animals, being with friends. I cannot do team sports. School is going well, and I feel at ease; I am learning to use the computer. Rethinking about the care pathway, I think everyone did what they could and what was right to do. When I think about tomorrow, I feel happy with the people who love me, and I would like everything to remain as it is now.

3.2. Narrative from an adult patient affected by an RPE65-related IRD

I don't remember a precise year, but the first signs that something was wrong were around the age of 6 or 7 when we were driving at night, and I realised that I couldn't see what my father needed to go. I could only see the light sources but not what they were illuminating. When I was 15 years old, I was driving back to the institute on Sunday afternoons; it got dark on the way, and I had a hard time walking from the station to the institute. If I had to walk together with other blind people, I would have done it with ease. I felt very uncomfortable, inappropriate, and inexplicably clumsy. In the evenings, I could not move to go out alone. If I accompanied other blind people, even two, I felt no discomfort, and the journeys went smoothly. I knew about my illness. I also met ophthalmologists who seemed to know less about it than I did. For the hope of treatment or recovery, ophthalmologists had already been consulted for my brother before I was born, or at least when I was small. While waiting for the diagnosis, I never had any expectations. When I learned that it was a hereditary disease, I was a child, and I had no reaction. I did the genetic test when I was 54 and, since I knew that there is a lot of retinitis, it was pure curiosity. Is it positive or negative to learn at 54 what exactly you have? Negative because it shows how much interest there is in such a disease: very little. It's good that research is going on, even if it's at a snail's pace. Only my mother has an attitude of some hope.

Having changed places I've gone to live [...] I have no way of comparing before and after. I never hid my problem, so they took me as I was. Seeing, even a little, even with difficulty, even when the amount of light allowed me to do things, "seeing" was, of course, more accessible. But since I knew that I would lose my sight sooner or later and that this took place over quite an extended period, I used these facts to run for cover, with the aim of not stopping. I liked cycling, which is different from riding a tandem bike, going out to look for glimpses of views, reading comics. The reading in black and the cycle rides gradually faded away. At school: I couldn't see the blackboard and do my homework alone. At work, as a teacher, I couldn't fill in the register by myself.
I only went for specific treatments for retinitis, useless but specific.
Today I feel the same as I did before. The disease has degenerated almost to the end. Functionally I am blind. Every now and then, I play the lamppost game, trying to catch the light from the lampposts as we walk down the street... in the evening.
When I go to the centre, I spend no less than 4 hours there, and 2 of them are waiting. So far, the people working there feel welcoming and helpful. So far, I've only had check-ups. I see gene therapy as an attempt to maintain the current faculties of the retina. We are still far from hoping for any kind of recovery, let alone a recovery measurable in tenths. I don't know why I've only had one visit to date where this therapy was mentioned for the first time. My family and I are on the same wavelength at the moment. So the family attends events to support my needs as they arise. I go to the swimming pool to do water gymnastics, with the others from our sports club we organise dinners in the dark. I have weekly music rehearsals with a group where only I am blind, we go to play in clubs, I go to see sculpture exhibitions if it is allowed to touch, of course. With my wife, who is also blind, we travel: when I have the chance, I like to get to know the cities, walking in their historical centres, alone. I read and listen to music. Unfortunately, I like to eat, so every opportunity is good to try a new restaurant. In everyday life, I am autonomous. Since there are many things I can do as a blind person, it seems useless to me to try at all costs to do something where sight is the only possibility. Like, for example: driving. I am autonomous in my activities; I only find difficulties when the computer aids are not adequate or modify the websites without considering the rules needed to include visually impaired users. I have been using personal assistants selected and trained by me for years in those areas where only sight works. Thinking back to my own care path, I would have liked to have had this care in the 1960s. My future is not conditioned by the presence of this care. But it seems worthwhile to me to do it: what will be, will be. We visually impaired people need civilisation. If in the behaviour of citizens, people, institutions, the observance of rules also prevails in the realisation of public and social things, we are in the right place. But in our society, this does not happen to a sufficient extent, so tomorrow will still be about making do as one can, with or without this care.

3.3. Narrative from a caregiver of a patient affected by an RPE65-related IRD

We toured the hospitals in our region. Visit after visit, the anamnesis and electrophysiological examinations were not sufficient for a diagnosis. Many signs and symptoms were confused between the different diseases affecting the retina. At six months, we realised that something was wrong with the involuntary eye movement, always searching for light, the lack of eye contact between

mother and child during breastfeeding. I felt an immense sense of absolute helplessness as a parent in front of her baby. I really needed to understand why... He is a very peaceful child; he plays, jumps, learns something new every day and knows how to give so much love. To understand what it was all about, we researched the subject because it helps us accept. I would see him and think that it's just a bad dream, with the hope of waking up to normality. We met very helpful and wonderful people.

When they told us that we needed to take a genetic test, I thought that there were no relatives with severe vision problems; it seemed so absurd. The genetic test was a simple saliva sample that allowed for greater accuracy; the genetic diagnosis was essential to know the gene that causes the disease. The wait for the diagnosis seemed like an eternity. The diagnosis, when it came, was a starting point; news like that turns your life upside down. He is a very calm child and learns every day to become more and more autonomous. When they told us that it was a hereditary retinal disease, I felt terrible because you don't expect it. It seems impossible to me to have a congenital disorder of a genetic nature in a family where there were no known cases. At that time, the environment was fundamental because I was more autonomous. At home, with the organisation of spaces, he moves on his own, and so he gets used to making do. He is friendly and loves being with other kids; he is cheerful, curious, and intelligent. There is a difference between seeing the light and not seeing it at all, so we are confident that everything has not degenerated. He likes to do everything, watch cartoons and knows some dialogues by heart. Among the activities he finds hard to do are playing football, drawing, playing basketball. As a parent, the only thing you want in life is to protect your children. It is challenging to live with this disease because I have mortifications in every area of life. We are waiting for the gene therapy to finally allow us to see the light at the end of the tunnel.

Today I feel very serene, and I never stop dreaming that after the discovery, the waiting, the hope, the light will finally come. Today he feels more peaceful, and day after day, he learns to be more vital to face his life. The disease is genetic, rare, incurable; we are healthy carriers of the defect and have passed it on to our son. The hospital that is treating us is a centre of excellence, and we have carried out the genetic test. Getting a diagnosis for a rare disease is not always easy. It is a long and tiring process. The time between checks is too long. For me, gene therapy would be the miracle we have been waiting for, as we are entering an era where diseases that were once incurable are becoming curable. Thanks to the love of those around him, he is learning to live with all the strength he needs. He is an adorable child and knows how to make others love him. He is a very healthy child who rarely gets sick. His eyesight is not yet very impaired; otherwise, he is very cheerful. Rethinking the care pathway, I would have liked to have had more information on this disease's knowledge, together with the proper psychological and educational support. If I had to imagine a service for all the people with the same disease as my son, I would think of a specialised centre for this disease, which could guarantee proper support for parents who face enormous difficulties. When I think of tomorrow, I don't know what awaits us. Still, we are very enthusiastic about the progress of science. I would like to see proper care centres and improved schooling for people with this disease in the future. Reading difficulties are essential, and there is a lack of adequate tools to deal with them.

3.4. Parallel chart on a patient affected by an RPE65-related IRD from a healthcare professional

Poor child: he is not living his life like his other healthy peers. The parents reported that they needed advice on how to make him as autonomous as possible. He could not play, run, be independent in his personal and school affairs. He could not orientate himself in space. The situation worsened from sunset onwards when the child panicked. The whole family hardly ever went out in the evening, not even for a simple dinner. I felt obliged to build a personalised rehabilitation programme to find alternative strategies to give the family tools and reassure the child to increase his self-esteem. I asked the child to tell me everything he wanted to do, everything he thought to do poorly, and his fears when he got stuck on various occasions. I asked the parents what they saw when they were with their child, their fears, their difficulties, what they wanted help with, what they hoped for. I gradually started to indicate how to organise the house according to the child's size, what light or contrast measures should be taken and how to organise the school material to make it more usable. It was not my job to communicate the diagnosis.

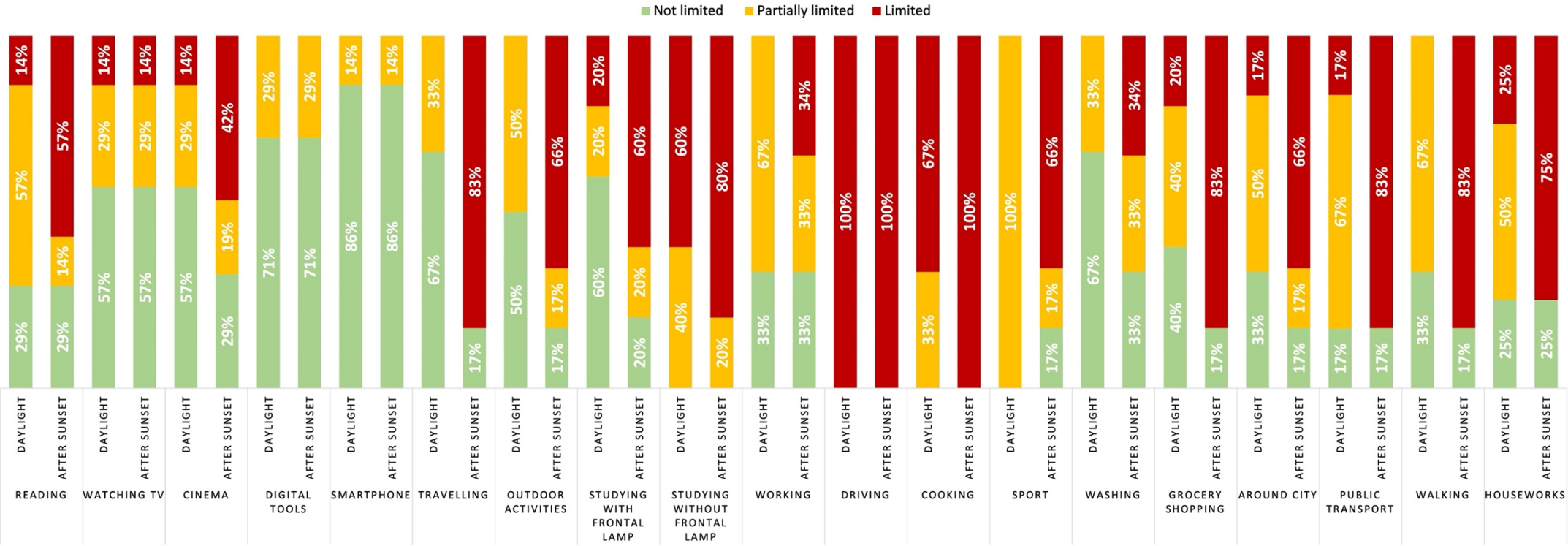
Other people often do not understand what and how he sees, so it ranges from denial to being overprotective. To see was not to fall, not to stumble, play football, watch television together with the family, write in the notebook without difficulty, and read without difficulty. The family was heartened and happy about the small degree of autonomy their child was able to achieve. The child began to experiment on his own without requiring the constant presence of others. When studying, the child felt frustrated because he realised that he could not write or read like the others. He felt different because he could not demonstrate his abilities and was frustrated because he could not keep up with others.

Today, he is more confident about himself, his abilities and also his limits. He has learned to set himself small goals, overcome them with his own alternative strategies and move forward. With other people, he is more present and less dependent. At school, he has found his own alternative methods to do almost the same as other peers; he participates more in the class group and verbalises his visual difficulties when he has a problem. The people around him seem more serene and confident in his potential. My aim is to make him aware of his challenges to face them with alternative strategies and overcome them even if with limitations. I feel stimulated to find with him alternative solutions to make him autonomous. I am learning from the caring relationship that there is no limit to the potential.

I would like to be able to help them even more in the future. I would like him to be aware of how extraordinary his will power is.

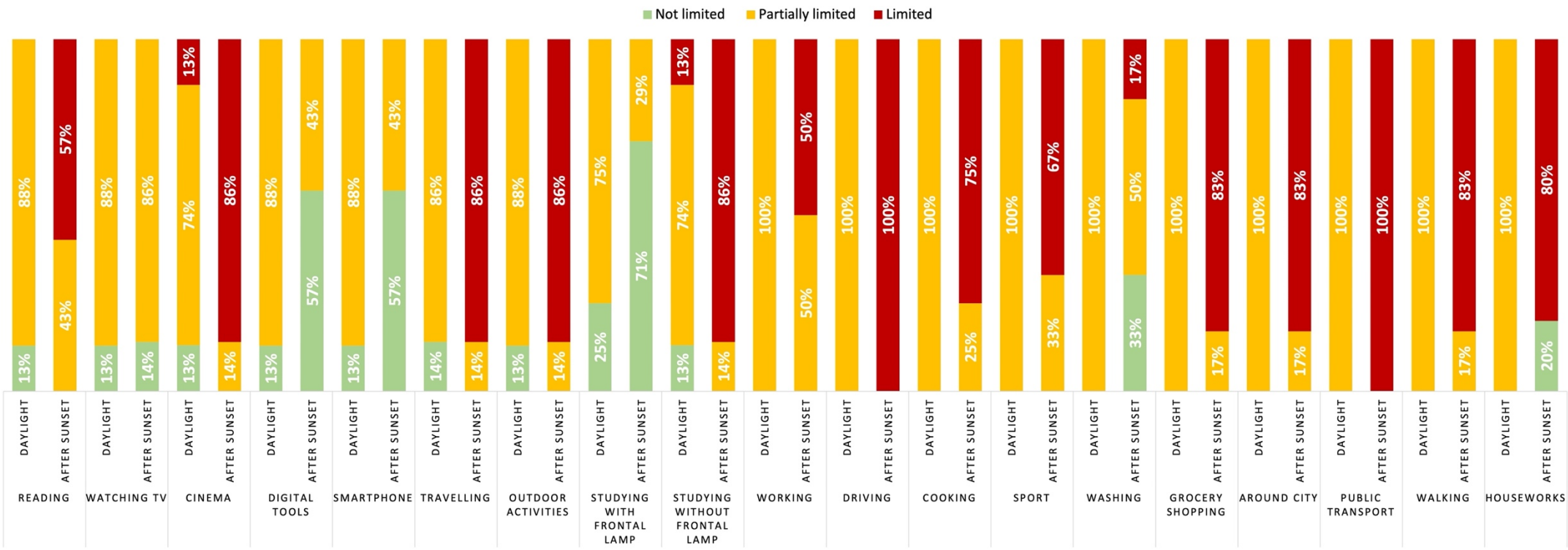
Supplementary file 4 – Reported limitations in activities by patients and caregivers

4.1. Patient self-reported limitations in activities before and after sunset (N=7*)



*Non-responses: 1.

4.2. Patient limitations in activities before and after sunset reported by caregivers (N=8)



Standards for Reporting Qualitative Research (SRQR)*

http://www.equator-network.org/reporting-guidelines/srqr/

	Page/line no(s).
Title and abstract	
Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	p. 1, ll. 1-3
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	p. 2, ll. 34-56
Introduction	
Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	pp. 3-4, ll. 64-91
Purpose or research question - Purpose of the study and specific objectives or questions	p. 4, ll. 92-101
Methods	
Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	p. 4, ll. 83-91
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	p. 6, ll. 135-136
Context - Setting/site and salient contextual factors; rationale**	p. 5, ll. 104-107
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	p. 5, ll. 113-116
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	p. 6, ll. 141-149
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	pp. 5-6, ll. 117-134

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	pp. 5-6, ll. 117-134
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	pp. 7-8, ll. 170-175
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	pp. 6-7, ll. 150-168
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	pp. 6-7, ll. 150-168
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	//

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	pp. 7-16, ll. 169-300
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	pp. 7-16, ll. 169-300

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	pp. 16-19, ll. 300-371
Limitations - Trustworthiness and limitations of findings	pp. 19-20, ll. 372-380

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	pp. 21-22, ll. 424-427
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	p. 22, ll. 428-429

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014
DOI: 10.1097/ACM.0000000000000388

BMJ Open

Narrative Medicine to investigate the quality-of-life and emotional impact of inherited retinal disorders through the perspectives of patients, caregivers, and clinicians: an Italian multicentre project.

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Narrative Medicine to investigate the quality-of-life and emotional impact of inherited retinal disorders through the perspectives of patients, caregivers, and clinicians: an Italian multicentre project.

Francesca Simonelli[1], Andrea Sodi[2], Benedetto Falsini[3,4], Giacomo Bacci[5], Giancarlo Iarossi[6], Valentina Di Iorio[1], Dario Giorgio[2], Giorgio Placidi[3,4], Assia Andrao[7], BIRDS Working Group, Luigi Reale[8], Alessandra Fiorencis[8], Manar Aoun[9]

"BIRDS – The Beat of IRD Stories" Working Group: Giovanni Bosco Vitiello[1], Amelia Citro[1], Simona De Simone[1], Irene De Rienzo[10], Natalia Filimonova[11], Stefania Fortini[12], Cristiana Marchese[7], Maria Giulia Marini[8], Dario Pasquale Mucciolo[2], Vittoria Murro[2], Ilaria Passerini[13], Simona Turco[12]

[1] Eye Clinic, Multidisciplinary Department of Medical, Surgical and Dental Sciences, University of Campania "L. Vanvitelli" – Naples, Italy

[2] Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence – Florence, Italy

[3] UOC Oftalmologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

[4] Università Cattolica del Sacro Cuore, 00168 Rome, Italy

[5] Pediatric Ophthalmology Unit, Children's Hospital "A. Meyer", University of Florence – Florence, Italy

[6] Ophthalmology Department, Bambino Gesù IRCCS Pediatric Hospital – Rome, Italy

[7] Retina Italia Onlus Association – Italy

[8] Healthcare Area, ISTUD – Milano, Italy

[9] Novartis Farma – Origgio, Italy,

[10] Department of Ophthalmology, Careggi University Hospital - Florence, Italy

[11] Novartis Pharma AG – Basel, Switzerland

[12] National Center of Services and Research for the Prevention of Blindness and Rehabilitation of the Visually Impaired, WHOCC ITA-100/Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy

[13] Department of Genetic Diagnosis, Careggi Teaching Hospital – Florence, Italy

*Corresponding authors: Luigi Reale, Healthcare Area, Fondazione ISTUD – via Paolo Lomazzo 19, 20124 Milano, Italy. Tel. +39 0323 933 801, Mobile +39 3484759910, e-mail: lreale@istud.it

Francesca Simonelli, University of Campania "L. Vanvitelli" – via S. Pansini 5, 80131. Tel. +39 081 5666607, e-mail: francesca.simonelli@unicampania.it

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ABSTRACT

Objectives. Although inherited retinal disorders (IRDs) related to the gene encoding the retinal pigment epithelium 65kD protein (RPE65) significantly impact the vision-related quality of life (VRQoL), their emotional and social aspects remain poorly investigated in Italy. Narrative Medicine (NM) reveals the more intimate aspects of the illness experience, providing insights into clinical practice.

Design and setting. This NM project was conducted in Italy between July and December 2020 and involved five eye clinics specialised in IRDs. Illness plots and parallel charts, together with a sociodemographic survey, were collected through the project's website; remote in-depth interviews were also conducted. Narratives and interviews were analysed through Nvivo software and interpretive coding.

Participants. Three paediatric and five adult patients and eight caregivers participated in the project; 11 retinologists globally wrote 27 parallel charts; five professionals from hospital-based multidisciplinary teams and one Patient Association member were interviewed.

Results. Findings confirmed that RPE65-related IRDs impact VRQoL in terms of activities and mobility limitations. The emotional aspects emerged as crucial in the clinical encounter and as informative on IRD management challenges and real-life experiences, while psychological support was addressed as critical from clinical diagnosis throughout the care pathway for both patients and caregivers; the need for an IRDs "culture" emerged to acknowledge these conditions and therefore promoting diversity within society.

Conclusions. The project was the first effort to investigate the impact of RPE65-related IRDs on the illness experience through NM, concomitantly addressing the perspectives of paediatric and adult patients, caregivers, and healthcare professionals and provided preliminary insights for the knowledge of RPE65-related IRDs and the clinical practice.

Keywords: inherited retinal dystrophies, *RPE65* gene, narrative medicine, illness experience, vision-related quality of life

STRENGHTS AND LIMITATIONS OF THIS STUDY

- Inclusion of paediatric patients' perspectives.
- Integration of patients' and caregivers' perspectives to that of retinologists and hospital-based multidisciplinary professionals.
- Participants did not equally represent the geographical areas of Italy.
- Restrictions due to Sars-CoV-2 pandemic impacted the number of patients visiting the clinics, so involved healthcare professionals had to engage them virtually.
- Patients and caregivers participated in the project on a voluntary basis, and Sars-CoV-2 pandemic could have created a bias on the motivation to join the research.

INTRODUCTION

Affecting about 1 in 2-3,000 people globally [1], Inherited Retinal Disorders (IRDs) constitute a group of clinically and genetically heterogeneous degenerative conditions in which gene mutations affect the proteins necessary to functional vision [2]. A progressive loss of photoreceptor cells and an impairment for visual function characterise the IRDs related to mutations involving the gene encoding the retinal pigment epithelium 65kD protein (RPE65) and gradually lead to an irreversible visual decline [3], and potentially to blindness [4]; Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP) represent the most common forms [5,6].

Age of onset ranges from early childhood to middle age; visual impairment at low light levels, night blindness and nystagmus are the early symptoms, followed by an increasing deterioration of visual acuity and peripheral vision [7]. While gene therapy represents a promising scenario for treating these conditions [3,8], IRDs management has been mainly support-oriented and focused on monitoring, counselling, and education [3].

RPE65-related IRDs significantly impact patients in daily activities [9], with implications for their sense of identity [10] and autonomy management [11]; previous studies associate visual impairment

with lower social engaging ability [12], self-confidence and vision-related quality of life (VRQoL) [13], as well as with higher levels of depression [14,15].

Against this backdrop, other studies and reviews [16,17] suggest that a holistic and multidisciplinary approach – also addressing IRDs emotional and social aspects – is crucial to support patients and their caregivers.

The World Health Organisation (WHO) has acknowledged narrative research as informative to address the illness experience [18] in leading clinical practice [19]; a keen focus on narratives resulted in better patient care also in clinical genetics practice [20]. As described in similar studies [21], Narrative Medicine (NM) is based on illness narratives [22] and aims to integrate the *disease*-centred approach, related to the biomedical sphere, with the *illness*- and *sickness*-centred approaches, focusing on the individual and social experience of a condition [23], respectively. NM addresses the possible interventions on a specific disorder by integrating the perspectives of all the actors involved in the care pathway [24], and its findings have been increasingly used to improve the quality of care in clinical practice [25,26].

The NM project "BIRDS – The Beat of IRD Stories" investigated the RPE65-related IRDs illness experience through the analysis of narratives (a) to reveal the practical, emotional, and social issues linked to these conditions as experienced by patients, caregivers, and healthcare professionals, and (b) to understand the patient's journey and expectations regarding the gene therapy, to finally provide insights to foster the knowledge on RPE65-related IRDs and clinical practice.

The present research article focuses on the first goal (a); another study addressed the second one [27]. Although other studies integrated the perspectives of both patients and caregivers [28, 29], to the best of our knowledge, this is the first project that also engages the retinologists and hospital-based multidisciplinary professionals (MDTs) in investigating the RPE65-related IRDs illness experience in Italy.

METHODS

Research design and setting

The project was conducted in Italy between July and December 2020 and targeted paediatric and adult patients with an RPE65-related IRD, their caregivers, retinologists and MDT professionals involved in their care pathway. Participants were enrolled from five eye clinics specialised in IRDs (Supplementary file 1) across Italy. In July 2020, the Steering Committee – composed of five retinologists working in these centres and a Patient Association (PA) member – participated in an online meeting conducted by researchers from Istituto Studi Direzionali (ISTUD), Healthcare Area to be trained in NM and to discuss the project's goals and design; the Steering Committee, together with other IRD specialists from these centres, were then invited to engage patients and caregivers in participating in the research by accessing the project's webpage http://www.medicinanarrativa.eu/birds.

A clinical RPE65-related IRD diagnosis, without a minimum length of follow-up time post-diagnosis, or the caregiving of a person with an RPE65-related IRD constituted the eligibility criteria for patients and caregivers, as well as the willingness to share their illness experience; however, the ability to write or communicate in Italian was critical for the inclusion.

Data collection

Researchers followed the Web Content Accessibility Guidelines (WCAG) 2.1 [30] to ensure survey accessibility. Patients were invited to share their narratives either by writing or recording an audio file; also, caregivers were allowed to support paediatric patients in writing their narratives following the project's data collection tools. Narratives were anonymously collected through the Alchemer platform, available on the project's webpage. Afterwards, raw narratives were downloaded as Microsoft Excel spreadsheets.

A sociodemographic survey and an illness plot [31], namely, a plot related to the illness experience, were addressed to patients and caregivers; evocative and open words characterised the illness plot to facilitate individual expression [32] and chronologically guide the narrative to identify changes over time. The retinologists' caring experience was gathered through the parallel chart [33], i.e., a personal notebook, parallel to the clinical one, in which to write down thoughts and feelings in a plain language [34]. The patients described in parallel charts could not coincide with patients participating in the project. Overall, these investigation tools (Supplementary file 2) addressed two common aspects: (a) the personal and social experience of RPE65-related IRDs from early symptoms onwards, and (b) the VRQoL perception and the current daily life with RPE65-related IRDs.

Furthermore, in-depth interviews [35] were conducted with MDT professionals involved in IRD care pathway and a PA member, caregiver of a person with an RPE65-related IRD, to facilitate the emergence of patient- and care pathway- related issues further and to delve into organisational aspects without proposing to these professionals the introspective experience of writing; the interviewees approved the transcripts before the analysis.

The investigation tools were designed by two ISTUD researchers with different academic backgrounds and reviewed by the Steering Committee to reduce any cognitive bias.

Patient and public involvement

Researchers did not engage patients and caregivers in (a) developing the research design and tools, (b) interpreting and discussing the results, and (c) contributing to the writing or editing of this document.

Ethical considerations

The project was performed according to the Declaration of Helsinki. Participants provided their web-based informed consent before their involvement and after being briefed on the project purposes and personal data processing procedures, according to the General Data Protection Regulation of

the European Union 2016/679 [36] and the Italian Law 196/2003 [37]. Furthermore, the IRD specialists involved obtained a written informed consent from the parents of paediatric patients during the first briefing on the project methods and purposes.

The Ethical Committee of the Luigi Vanvitelli University Hospital (Naples, Italy) approved the project in September 2020 (protocol ID 20964/2020).

Analysis

Researchers analysed the sociodemographic data through descriptive statistics; answering survey questions or filling in fields in the illness plots and parallel charts was not mandatory, so sample size may vary. Narratives were entered into Nvivo software [38] for coding and content analysis [39]. Three narratives for each group and one in-depth interview were collectively coded to assess the consistency across team members; then, each narrative and in-depth interview were separately coded and reviewed during weekly peer debriefings to limit any interpretation bias.

Open interpretive coding was employed to identify and analyse the emerging contents in all narratives and in-depth interviews. Moreover, adult patients' and caregivers' narratives and parallel charts were classified following: (a) Kleinman's classification [23], which identifies *disease-*, *illness-*, and *sickness*-related aspects in narratives, respectively concerning the biomedical description of a condition, its personal and emotional experience, and its social and cultural perception; (b) Bury's classification [40], which distinguishes among *contingent narratives* (concerning a condition's immediate effects on daily life), *core narratives* (connecting the illness experience to deeper and cultural levels of meaning) and *moral narratives* (highlighting an evaluative and social dimension). Researchers did not apply retrospective classifications of narratives to paediatric patients' narratives since their caregivers' in-writing support could have affected the narrative style and the word choice.

Researchers asked the participants to describe RPE65-related IRDs through a metaphor to trace spontaneous meaning associations related to the illness experience through daily language [41]. The Steering Committee discussed the results to address the emerged issues and data interpretation collectively. Researchers followed the Standards for Reporting Qualitative Research (SRQR) guidelines [42].

RESULTS

Three paediatric and five early-onset adult patients and eight caregivers participated in the project, as well as 11 retinologists specialised in IRDs, who wrote 27 parallel charts; all patients chose to share their experience in writing. In-depth interviews were conducted with five MDT professionals – i.e., two genetic counselors, two psychologists and one orientation and mobility (O&M) instructor – and one PA member. Table 1 summarises the sociodemographic data of participants, including non-responders as a separate category.

Table 1 – Sociodemographic data of participants

	Patients (N=8)	Caregivers (N=8)	Patients in parallel charts (N=27)	Retinologists (N=11)	Participants in in-depth interviews (N=6)
Gender					
Female	6 (75%)	6 (75%)	12 (44%)	5 (45%)	5 (83%)
Male	2 (25%)	2 (25%)	15 (56%)	6 (55%)	1 (17%)
Age (yrs)					
Median (range)	26 (8-63)	44 (31-70)	17 (5-65)	42 (32-64)	54 (49-67)
Geographic residence					
Northern Italy	3 (38%)	2 (24%)	-	-	2 (33%)
Central Italy	4 (50%)	4 (50%)	-	8 (73%)	4 (67%)
Southern Italy	1 (12%)	1 (13%)	-	3 (27%)	-
Non-responders	-	1 (13%)	-	-	-
Education					
Elementary school	1 (12%)	-	7 (26%)	-	-
Middle school	-	1 (12%)	4 (15%)	-	-
High school	1 (12%)	3 (38%)	4 (15%)	-	-
Bachelor/Master	3 (38%)	3 (38%)	3 (11%)	-	-
Non-responders	3 (38%)	1 (12%)	9 (33%)	-	-
Employment status					
Student	4 (50%)	-	16 (59%)	-	-
Working	3 (38%)	6 (76%)	10 (37%)	-	-

Not working	-	-	-	-	-
Retired	-	1 (12%)	1 (4%)	-	-
Non-responders	1 (12%)	1 (12%)	-	-	-
Marital state					
Single	6 (75%)	1 (12%)	18 (67%)	-	-
Married	2 (25%)	5 (64%)	7 (26%)	-	-
Separated	-	1 (12%)	2 (7%)	-	-
Non-responders	-	1 (12%)	-	-	-
Professional activity (yrs)					
Median (range)	-	-	-	16 (6-41)	23 (19-35)
Specialisation					
Ophthalmology	-	-	-	8 (73%)	1 (17%)
Paediatric ophthalmology	-	-	-	1 (9%)	
Orthoptics	-	-	-	2 (18%)	
Medical Genetics					1 (17%)
O&M Training					1 (17%)
Psychology					2 (32%)
Other	-				1 (17%)
Workplace					
Hospital	-	-	-	2 (18%)	
University Hospital	-	-	-	9 (82%)	2 (33%)
Other					4 (67%)

Data are presented as n(%) or median (range).

Results are presented along four main lines: (a) the RPE65-related IRDs experience analysed through narrative classifications and metaphors; (b) the emotional issues before and upon the clinical diagnosis; (c) VRQoL perception, the condition's impact on daily life and participants' expectations; (d) insights from in-depth interviews. Narratives informed (a) and (b), while (c) was investigated through both narratives and quantitative data from the survey; in-depth interviews alone informed (d). Figures 1-3 and Tables 2-5 provide quotes from the narratives, while four narratives are available in English in Supplementary file 3; we reduced the risk of re-identification by applying different codes from those used to identify participants during data collection.

The RPE65-related IRDs experience in the narratives

Overall, almost all classified narratives highlighted illness-related aspects [23] (Figure 1); adult patients' narratives lacked a clinical language, which conversely characterised 63% of the caregivers' narratives and 37% of the parallel charts. Sickness-related issues were present in 50% of the

caregivers' narratives and in 11% of the parallel charts, while they emerged in all adult patients' narratives.

[Figure 1]

Core narratives [40] prevailed in parallel charts (74%) and were equally reported (50%) as moral narratives by caregivers (Figure 2); only parallel charts presented contingent narratives (11%). Moral narratives were prevalent among adult patients (60%), while discomfort, disbelief (particularly at school) and the search for independence represented three spontaneously emerged issues in all narratives.

[Figure 2]

Metaphors were clustered into four thematic groups (Figure 3): (a) those referring to light and hope, used by patients (33%) and in parallel charts (15%); (b) those concerning limitations and impairment, equally reported (50%) by patients and caregivers; (c) those related to darkness and mist, used by caregivers (33%) and in parallel charts (40%); (d) and metaphors denoting pain and isolation, almost equally used by patients and caregivers, and in parallel charts.

[Figure 3]

Emotional issues upon the clinical diagnosis and the clinical encounter

Patients reported having had the first signs of visual impairment at two years and three months of age (median value; range 0,5-6). In narratives, all patients reported issues that arose during early childhood, and that their parental caregivers identified as critical, e.g., being attracted by light sources or tripping (*In the evening, my parents used to cover the kitchen lamp, otherwise I would spend hours just staring at it*, Patient 002). As shown in Table 2, patients described early living with an RPE65-associated IRD either as uncomfortable (62%), mainly referring to the feeling of "being wrong", caused by the informal tests or eye examinations they were subjected to by their parents, or – conversely – normal (38%), since they did not have any standard of comparison to evaluate

their sight. Caregivers reported having felt worried (50%) or helpless (50%) in the same years. During the communication of the clinical diagnosis, 71% of patients had no reaction, while the other 29% reported that it allowed them to identify their condition; conversely, parental caregivers (75%) felt hopeless, while partner caregivers (25%) reported concern for the hereditariness of the condition.

Table 2 – Patients' and caregivers' emotions before and at the diagnosis of RPE65-related IRD

Patients		
Before diagnosis	Normal (38%)	*– I have always felt normal. I never had the feeling that the slight differences I noticed could be a problem, or part of a problem*. (Patient 004)
	Uncomfortable (62%)	*– I felt their disappointment, their concern... They were not happy with me, and I felt wrong, because my answers were wrong. I couldn't see, and I couldn't help but guess...* (Patient 002)
At diagnosis	Identification (29%)	*– Somehow, finally identifying the problem brought me out of my limbo: for years, I had been the child who saw little during the day and who couldn't see at night; now I finally knew why. I became familiar with terms such as "blindness", "low vision", or "disability", concepts that would later radically change my future*. (Patient 001)
	Neutral (71%)	*– Honestly, I wasn't much affected. The disease has always been part of me. I grew up with it, I gradually got used to it*. (Patient 004)
Caregivers		
Before diagnosis	Worry 50%	*– I felt helpless, terrified, and afraid*. (Caregiver 003)
	Helplessness 50%	*– I felt terrible, because I understood the challenge, but I couldn't do much, except hold her hand*. (Caregiver 006)
At diagnosis	Hopelessness 75%	*– I felt terrible. It's something you don't expect: a hereditary disease of a genetic nature in a family where there were no known cases seems impossible*. (Caregiver 008)
	Fear for children 25%	*– In the beginning, it scared me: the fear that our other children could suffer from a similar condition. Our anxiety decreased with time: I saw her, I saw she was restricted but not blocked, which gave me courage*. (Caregiver 005)

Table 3 summarises the clinicians' feelings the first time they met their patients and at the beginning of the care pathway. During the first visit, 37% of parallel charts reported the thought that the path would have been challenging, while 30% reported hopefulness over the care options; conversely, 22% focused on a sense of sorrow for the patient, and 11% on the empathy with patients or caregivers. At the beginning of the care relationship, clinicians felt on one side emotionally involved

or motivated to do their best (58%), and on the other side helpless (30%) or "guilty" for being in a privileged situation compared to the patient (12%).

Table 3 – Retinologists' emotions at first visit and at the beginning of the care relationship

At the first visit	A challenge for both clinician and patient 37%	*– I thought that this visit was a challenge for us both: for her, it meant undergoing new tests and knowing the results; for me, it meant dedicating myself to another person to whom I could dedicate my care. I also thought that she might have access to treatment in the future, and I was ready and willing to facilitate this*. (Parallel chart 007)
	Hope 30%	*– I thought it was essential to follow her carefully from a clinical perspective, and that it was imperative to have a genetic test. When she showed it to me, I realized that she had a treatable mutation, which gave me hope*. (Parallel chart 015)
	Sorrow 22%	*– Poor child, he is not living his life like his healthy peers*. (Parallel chart 002)
	Empathy with patient or caregiver 11%	*– I thought that he was the same age as me, but that he had a completely different visual situation from mine. I stepped out of the treating doctor's shoes, and I found myself projected into an essentially human dimension. I put myself in her shoes and listened to her story with my heart as well as my ears*. (Parallel chart 006)
At the beginning of the care relationship	Emotional involvement and motivation 58%	*– I was impressed by what I was seeing, powerless but at the same time full of motivation and hope. I knew the child's mutation, and I imagined that – given his young age – he might have a therapeutic chance. I leveraged this last point in my talk with his parents, trying to give them a cautious hope and making them understand that this specific genetic mutation meant being severely visually impaired, but also the possibility of being cured in a not distant future*. (Parallel chart 005)
	Helplessness 30%	*– Despite my knowledge, I felt powerless, unable to give immediate and concrete answers to many of his practical problems*. (Parallel chart 019)
	Sense of guilt 12%	*– I felt ashamed... I'm lucky, I think I have a successful life, and yet I often get irritated or discouraged by stupid things, while he always seems happy to live his life, despite everything*. (Parallel chart 021)

In addition, 33% of the parallel charts highlighted the importance of showing empathy from the very beginning of the care relationship.

As for the currently living with an RPE65-related IRD (Table 4), patients reported a sense of uncertainty (25%), due to increasing visual impairment, or discomfort and sadness (25%); conversely, 50% reported to feel serene or hopeful, also considering the possibility of undergoing gene therapy. Caregivers declared to have accepted the condition (38%) and to live more serenely (62%), due to the awareness of having done their best. In parallel charts, clinicians reported positive feelings (44%), dedication (37%), and motivation (19%) toward patients.

Table 4 – The current feelings of participants: distribution and quotes from narratives

	Patients
Uncertainty 25%	*– Today I feel poised between light and shadow. I feel like someone who chases a ball without ever reaching it. I am 42 years old, and I have spent my life being told that science works miracles, and that life is long, and that progress for me will come soon. I am 42, though, not 10… My sight is progressively worsening. I feel tangible differences over a few months, days in some cases. I can remember things from a few months ago, visual details that I no longer see today. In fact, it's not that I don't see them: I perceive them as covered by a veil. Glossy... Like old photographs, but far less poetic...* (Patient 001)
Discomfort, sadness 25%	*– I feel sad: when mum or dad are driving, in the afternoon or in the evening, I do not see the road, I only notice a few lampposts*. (Patient 007)
Serenity, hope 50%	*– Today I feel hopeful for the future. I try every day to accept my challenges and to live with serenity. If the situation gets worse, I know that I will have to find different ways. It will be hard, maybe even unpleasant, but it will be possible. If the situation improves, thanks to gene therapy, I will be pleased*. (Patient 002)
	Caregivers
Acceptance 38%	*– I feel I am an integral part of my son's life. I live in symbiosis with him. Everything is more manageable: I manage to find solutions quite easily to meet his needs during his constant difficulties. Let's say that everything is always about having an obstacle to overcome... It's never easy, and sometimes it's mentally exhausting*. (Caregiver 003)
More serenity 62%	*– I know that we are doing our best to understand her condition better and, if possible, to start the therapy. The knowledge that we are doing our best brings me serenity*. (Caregiver 005)
	Retinologists
Positive feelings 44%	*—I'm feeling comfortable. Able to do my job without hiding my human side. Open to questions and ready to give competent and precise answers. Willing to help but aware of my limits, my role, and my possibilities*. (Parallel chart 006)
Commitment 37%	*—I feel obliged to give him what he hasn't had so far*. (Parallel chart 012)
Motivation 19%	*—I realize that it is a mutual gift. It reassures me to see her grow strong and able to face tomorrow despite her condition. I feel good with her, comforted by her positive attitude*. (Parallel chart 010)

VRQoL perception and daily living with RPE65-related IRDs

Supplementary file 4 presents survey data on patients' and caregivers' evaluation of RPE65-related IRDs impact on patients and their day-to-day tasks in relation to low light conditions; Figure 4 provides an overview of essential data.

[Figure 4]

Patients reported an increasing impact on main daily activities after sunset; thus, they referred both a severe impact on driving (100%) and cooking (100%), and no impact on the use of smartphones (86%) regardless of light conditions. Caregivers reported higher levels of limitation for patients in

some activities even before sunset, such as reading, using digital tools or smartphones, washing, moving around; however, they reported fewer limitations in driving and cooking before sunset (100% *partially limited*). Considering an open coding of VRQoL domains in patient narratives, the limitation in activities was the prevalent issue, concerning 100% of patients' narratives. Mobility limitation (–*The city becomes more and more hostile. I am afraid of tripping, bumping into things, hurting myself, taking a wrong turn, being followed, and having to flee from a danger without being able to do so*, Patient 001), health concerns (–*I am sad and cry. I ask my mother if my eyes will ever be able to see well*, Patient 007) and emotional well-being issues (–*I cannot accept that I cannot do many things anymore, and I cannot admit that this leads me to close myself off*, Patient 006) emerged in 75% of patients' narratives.

Nevertheless, further survey data showed that 72% of patients considered their VRQoL good, and 14% excellent (Figure 5); thus, they reported that RPE65-related IRDs have enough impact on the performance of their daily activities (83%). Fifty percent of caregivers defined their patient's VRQoL acceptable, and only 38% good; conversely, 30% and 14% reported that RPE65-related IRDs have a low – or no – impact on patients' performance of daily activities, respectively.

[Figure 5]

Addressing future perspectives, 71% of patients reported their hope to live serenely, both within their family and in the social context (–*I just want my loved ones to see me calm and serene. […] I could not bear to see my relatives feeling bad for me*, Patient 006), and 29% their hope to receive gene therapy (–*Thinking about tomorrow, I would like to receive gene therapy*, Patient 002); caregivers also stated to await gene therapy (50%). Clinicians hope to maintain a high quality of care in 41% of parallel charts, to improve their interpersonal skills and therapeutic possibilities for patients in 37%, and to be able to give them real hope in 22% (–*Sometimes I think that gene therapy*

has already become a reality, and I feel that I am living a surreal experience. […] I wish that what I perceive as surreal today soon becomes reality, Parallel chart 007).

Overall, participants described writing as a positive experience: 80% of patients reported that narrative was a positive experience, and 20% stated to have felt a sense of freedom in sharing the illness experience. Twenty-seven percent of the caregivers' narratives and 21% of the parallel charts reported to consider it useful to raise awareness about these conditions; however, they also highlighted negative feelings, such as fatigue or sadness, in 14% and 8% of cases, respectively.

Insights from in-depth interviews

Five macro-themes transversely emerged from the in-depth interviews with MDT professionals and PA member (Table 5):

(a) The O&M instructor described the gap occurring between early-onset patients, who can develop compensatory strategies over time, and adult-onset patients, more likely to lose their previous visual experience. Thus, early-onset patients may experience their sight as "normal"; in this sense, the psychologists highlighted the importance to psychologically support patients upon the communication of the clinical diagnosis, when introducing the notion of "impairment".

(b) According to all interviewees, psychological support should be provided throughout the care pathway to improve communication and avoid misleading messages that could make patients feel that they "could do nothing more". Furthermore, as also maintained by the genetic counselors and the PA member, a more careful communication would allow the patient to keep an active perspective on the care pathway and early address rehabilitation programs.

(c) All interviewees addressed the RPE65-related IRDs impact on parental and partner caregivers. While the latter may face a couple crisis due to the progression of the

impairment, the former often deal with the failure of the "perfect child" dream, the hope that their children will heal and a strong sense of guilt for the inheritability of the condition. Since caregivers project these complex feelings on patients, potentially impacting their care pathway, a psychological support should be provided to help them accept this condition.

(d) All interviewees highlighted the lack of knowledge of IRDs among the general public and society. The O&M instructor stressed that the link between visual impairment and changing light conditions is challenging for those who do not know these diseases. The psychologists confirmed that this is also critical in the school environment. One psychologist and the PA member mentioned the need to create an IRDs "culture" and to address the diversity issue.

(e) Furthermore, one psychologist focused on the need for investigation tools integrating quantitative questionnaires to address the interpersonal dimension of daily activities, especially after sunset or in low light conditions.

Table 5 – Macro-themes reported by MT professionals and PA representative interviewed: quotes from in-depth interviews

Managing IRDs	– *In some people, the degenerative process begins during adulthood. They "unconsciously" erase all their previous visual experiences: it's a psychological reaction to the condition. Thus, they really need a "carer" because they can no longer do anything. Their mind forgets and cannot retrieve all the skills they possessed before from their store of experiences. On the other hand, in children who are used to this type of vision from an early age, visual function adapts, even if it gradually diminishes. They can create compensatory strategies more quickly, even if, while working on it, we realize that their visual acuity or visual field have worsened*. (Interviewee 002)
Communication of the diagnosis	– *[...] Colleagues who are not familiar with this condition are sometimes caught off guard. In the past, there have been communication issues. [...] Over the years, I have seen everything: from diagnoses not being communicated even when clear and evident, to children being told to learn Braille. Sometimes prognoses were communicated incorrectly; patients perceived them as crude, or they were told not to have children, because they would all be suffering from the same condition.* (Interviewee 001) – *We still have situations where the diagnosis is communicated violently: unfortunately, there is no cure for the disease, blindness could occur, but we do not know when... Verbal violence is where any kind of hope is taken away. [...] The main issue after the diagnosis is the psychological one. Suppose the diagnosis is communicated together with the possibility of recuperation, in which case one can deal with it somehow; but if it is expressed without this possibility, people don't even undergo check-ups anymore*. (Interviewee 004)
Attention to partner and parental caregivers	– *Some couples, [...] when they discovered the condition experienced a crisis. [...] What I noticed is that the way a caregiver treats his/her partner changes a lot: It's more imperative* (Interviewee 002)

	– A parent cannot serenely accept the condition of a child. Mothers are confronted with this issue daily, i.e., they are considered "good mothers" if they can accept it, and this translates into the thought "I am not a good mother, I will not be a good mother". [...] These parents often call the child "sick". Disability is not a disease, but a condition. In pregnancy, parents expect to have a "healthy" child: the hope is to regain this healthy child, even when it is objectively impossible. (Interviewee 003)
Lack of knowledge of IRDs	*– In terms of daily life, people with this condition experience uncertainty, which is not even daily, but hourly. They may not see the same things at 10:00 and 10:30 am, because of a series of parameters that come into play: size, permanence, brightness, which give the retina a different visual function. So, this uncertainty generates other insecurities, and often triggers profound depressive states. This is not understood by other people. Often, at school, teachers do not understand how the child could see the blackboard at the beginning of the lesson and not at the end. The explanation is evident to those who know these disorders: maybe the sun's angle had changed, of fatigue may come in to play, together with a series of parameters that determine a visual loss*. (Interviewee 002) *– I believe that initiatives are needed to allow people gain experience. For children, we could think of initiatives in school, which should be carried out regardless of the presence in the class of a child with this condition. We need to create a "culture" [...], a culture of confrontation with diversity*. (Interviewee 003)
New investigation tools	*– The dimension of being with others is entirely missing: all activities are investigated as if they were carried out by the person alone, but rarely people with this condition are alone, especially after sunset*. (Interviewee 003)

DISCUSSION

The project represents the first effort to investigate RPE65-related IRDs in Italy through NM, simultaneously addressing the perspectives of patients, caregivers and treating retinologists and collecting insights from MDT professionals and PA members.

The co-presence of *illness*- and *sickness*-related aspects [23] and the lack of a clinical language in patient narratives highlighted the centrality of the personal and social dimensions of living with an RPE65-related IRD in narrating the illness experience and trying to make sense [10] of the condition; the prevalence of moral narratives [40] supports this suggestion. The employed classifications allowed related themes to emerge in narratives spontaneously: patients declared to have manifested the first signs of visual impairment during early childhood and reported a discomfort mainly due to the informal testing they were subjected to by their parents, together with repeated eye examinations, before the clinical diagnosis; at school, their visual impairment is misunderstood or questioned by their teachers, who are not aware of the relationship between visual impairment

and changing light conditions. In-depth interviews confirm the lack of knowledge about IRDs among the general public and society, as well as at school, where patients also experience stigma [43] since their visual issues are addressed like cognitive impairments. Further investigations on the school environment may integrate studies on the patients' discrimination at their workplace [44] and studies on the patients' feeling of being often patronised [10].

Early-onset patients perceive their sight as "normal", finding out to be "impaired" only after the clinical diagnosis or by interacting with their peers in the school environment. As emerged from the in-depth interviews, the notion of "impairment" should be carefully introduced to support the patients' awareness of their condition. This issue may be further explored and integrated with studies on making sense and coping with IRDs [10, 12], while careful communication should be adopted throughout the care pathways.

The search for autonomy emerges as related to the health concerns for the progressive sight loss and the emotional well-being issues showing anxiety for the future. Findings confirm that RPE65-related IRDs significantly impact patients' VRQoL in terms of activity and mobility limitations: while changing light conditions do not change the use of digital tools or smartphones, activities such as driving and cooking remain challenging, regardless of the light conditions; moreover, the capability to perform daily activities is compromised by low light conditions, as also shown in studies addressing IRD critical effects on lifestyle choices [11, 45]. Nonetheless, many patients reported having a good VRQoL, suggesting that they have found strategies to cope with the condition in the absence, so far, of a therapeutic solution; these coping strategies should be further investigated. Two considerations may be emphasised. On the one side, the narratives and survey data show misalignment between the patient's and the caregiver's perception of the former's limitation in activities and in VRQoL, where patients report a higher perceived VRQoL, and conversely a lower performance while carrying out daily tasks: we remark that patients' coping strategies may

represent a possible explanation and – at the same time – not visually impaired caregivers may have a different perception of IRD impact on patients' life; however, this issue needs further investigations. On the other side, the search for autonomy is linked with the perception that relying on others is a limitation, confirming previous studies on this topic [11].

The metaphors used by patients to describe RPE65-related IRDs highlight not only limitations and pain, but also lights and hope. Conversely, the association with images recalling darkness emerges from caregiver narratives and parallel charts; in particular, caregivers do not use any positive image to describe RPE65-related IRDs.

In contrast with patients, caregiver narratives largely focus on *disease*-related aspects [23]; however, the presence of *sickness*- and *illness*-related aspects suggests their emotional commitment to the patient's well-being. Furthermore, moral narratives [40] reveal the sense of guilt experienced by caregivers about the hereditariness of the condition, which is also addressed within in-depth interviews: while partner caregivers may face a couple crisis upon the onset of the condition, parental caregivers experience the failure of the "perfect child" dream and struggle to accept the condition. Misalignment in the patients' perception of their VRQoL, metaphors, and the emotional issues reported also suggest the complexity found by caregivers in coping with these conditions.

Parallel charts show that retinologists are personally and emotionally involved in the care relationship, as suggested by the prevalence of core narratives [40] and reported their feelings at the beginning of the care pathway, despite being less focused on social RPE65-related IRDs aspects. Retinologists emerge as being motivated to find the most suitable therapeutic pathway, as well as emotionally committed to patients; for the first time in similar NM projects, clinicians report a clear sense of guilt for being "healthy" compared to their patients.

These are only preliminary findings; however, they can provide initial insights on the importance of a multidisciplinary RPE65-related IRDs clinical practice:

(a) RPE65-related IRDs critically impact several quality-of-life domains, while the emotional aspects of RPE65-related IRDs emerge as crucial while making sense of the condition and during the clinical encounter: the tension between the individual and the social dimensions of these conditions emerged as informative of the care pathway challenges and real-life experiences, and may be better addressed through new investigation tools, as claimed by the in-depth interviews. The NM approach has proved suitable for this purpose since sharing the illness experience by writing allows for more introspective and reflective knowledge, that may integrate the one-to-one level of in-depth interviews used in researching the living with a certain condition.

(b) The emotional burden of caregiving remains poorly investigated. Nonetheless, narratives show that caregivers deeply participate in the patient's illness experience, while the in-depth interviews recommend a psychological support to help them accept the condition, while potentially improving the care pathway.

(c) The need for an RPE65-related IRDs "culture" emerges as crucial to acknowledge these conditions, to avoid perpetuating the stigma and the scepticism and to foster the debate on diversity at society level.

Since narratives were anonymous, we are not able to precisely state the misalignment between patients and caregivers regarding the performance of daily activities and the perception of VRQoL; moreover, the voluntary participation in the project may have constituted a selection bias and included mostly patients more comfortable with writing. Further investigations are needed to examine in more details the issues which spontaneously emerged, also involving the work sphere. The annual incidence of RPE65-related IRDs explains the low number of participating patients [46];

however, the narratives collected suggest a strong dedication to the project and a relationship of trust between patients, caregivers and the retinologists from the centres involved. Finally, the data collection phase partially coincided with the local measures decided by the Italian government to contain the Sars-Cov-2 pandemic, with consequences on the clinical follow-up and the participation in the project.

CONCLUSION

The project investigated the practical and emotional issues of RPE65-related IRDs as experienced by patients, caregivers, and retinologists, and provided insights from MDT professionals and PA members. It represented the first Italian project that simultaneously addresses and integrates these perspectives, whose comparison allowed to provide preliminary suggestions useful for the clinical practice and the knowledge of RPE65-related IRDs. NM allowed to connect the impact of RPE65-related IRDs on quality-of-life domains with real-life experiences, emerging as informative in raising suggestions to improve the care pathway for these conditions.

Abbreviations

IRDs – Inherited Retinal Disorders

RPE65 – Retinal pigment epithelium-specific 65 kDa protein

LCA – Leber congenital amaurosis

RP – Retinitis Pigmentosa

VRQoL – Vision-Related Quality of Life

WHO – World Health Organization

NM – Narrative Medicine

MDTs – Multidisciplinary teams

PA – Patient Association

WCAG – Web Content Accessibility Guidelines

SRQR – Standards for Reporting Qualitative Research

DECLARATIONS

Ethics approval

The project was conducted according to the Declaration of Helsinki. The Ethical Committee of the Luigi Vanvitelli University Hospital (Naples, Italy) approved the project rationale, design, investigation questionnaires and informed consent in September 2020 (protocol ID 20964/2020).

Consent to participate

Participants provided a web-based informed consent before their involvement and after being briefed on the purposes of the research and the procedures for the processing of personal data, according to General Data Protection Regulation of the European Union 2016/679 and the Italian Law 196/2003. The clinicians involved obtained a written informed consent to participate from the parents of underage patients during the first briefing on the project's methods and purposes.

Consent for publication

Not applicable.

Data sharing

All datasets used and analyzed during the current research are available in Italian from the corresponding author, upon reasonable request.

Competing interests

MA and NF are employees of Novartis Pharmaceuticals, Italy, and Region Europe. FS, BF, GB, and GI have received honoraria from Novartis Pharmaceuticals, Italy, for holding webinars. FS, AS, IP, IDR have received honoraria from Novartis Pharmaceuticals, Italy, for serving on advisory boards.

Funding

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Authors' contributions

FS, AS, BF, GB, GI, AA, LR, NF and MA were involved in the project's conceptualization. MGM, LR, and AF were involved in the methodology. FS, AS, BF, GB, GI, VDI, DG, GP, AA, GBV, AC, SDS, IDR, SF, CM, DPM, VM, IP and ST contributed to the project's investigation. RL and MA were involved in the project's administration. LR and AF contributed to data analysis. FS, AS, BF, GI, VDI, DG, GP, AA, LR and MA contributed to data validation. AF, LR and MA were involved in writing; all authors contributed to the manuscript review and read and approved the final draft for submission.

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References

1. Broadgate S, Yu J, Downes SM, Halford S. Unravelling the genetics of inherited retinal dystrophies: Past, present and future. *Progress in Retinal and Eye Research*. 2017; 59.
2. Ziccardi L, Cordeddu V, Gaddini L, Matteucci A, Parravano M, Malchiodi-Albedi F, et al. Gene therapy in Retinal Dystrophies. *In J Mol Sci*. 2019 Nov 14; 20(22).
3. Kang C, Scoo LJ. Voretigene Neparvovec: A Review in RPE65 Mutation-Associated Inherited Retinal Dystrophy. *Mol Diagn Ther*. 2020 Aug; 24(4).
4. Duncan JL, Pierce A, Laster AM, Daiger SP, Birch DG, Ash JD, et al. Inherited retinal degenerations: Current landscape and knowledge gaps. *Transl Vis Sci Technol*. 2018;7.
5. Tsang SH, Sharma T. Leber Congenital Amaurosis. *Adv Exp Med Biol*. 2018; 1085.
6. Tsang SH, Sharma T. Retinitis Pigmentosa (Non-syndromic). *Adv Exp Med Biol*. 2018; 1085.

7. Jacobson SG, Aleman Ts, Cideciyan AV, Roman AJ, Sumaroka A, Windsor EA, et al. Defining the residual vision in Leber congenital amaurosis caused by RPE65 mutations. Invest Ophthalmol Vis Sci. 2009 May; 50(5).
8. Russell S, Bennet J, Wellman JA, Chung DC, Yu ZF, Tillman A, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet. 2017 Aug 26;390(10097).
9. Thompson DA, Ali RR, Banin E, Branham KE, Flannery JG, Gamm DM, et al. Advancing therapeutic strategies for inherited retinal degeneration: recommendations from the Monaciano Symposium. *Invest Ophthalmol Vis Sci*. 2015;56(2).
10. Thurston M, Thurston A, McLeod J. Socio-emotional effects of the transition from sight to blindness. *British Journal of Visual Impairment*. 2010; 28(2).
11. Prem Senthil MP, Khadka J, Pesudovs K. Seeing through their eyes: lived experiences of people with retinitis pigmentosa. Eye. 2017;31(5).
12. Bittner AK, Edwards L, George M. Coping strategies to manage stress related to vision loss and fluctuations in retinitis pigmentosa. Optometry. 2010; 81(9).
13. Lloyd A, Piglowska N, Ciulla T, Pitluck S, Johnson S, Buessing M, et al. Estimation of impact of RPE65-mediated inherited retinal disease on quality of life and the potential benefits of gene therapy. *Br J Ophthalmol*. 2019 Nov;103(11).
14. Chacón-López H, Pelayo FJ, López-Justicia MD, Morillas CA, Urena R, Chacon-Medina A, Pino B. Visual training and emotional state of people with retinitis pigmentosa. J Rehabil Res Dev. 2013;50.
15. Kempen GI, Ranchor AV, Ambergen T, Zijlstra GR. The mediating role of disability and social support in the association between low vision and depressive symptoms in older adults. *Qual Life Res*. 2014; 23(3).
16. Parmeggiani F, Sato G, De Nadai K, Romano MR, Binotto A, Costagliola C. Clinical and Rehabilitative Management of Retinitis Pigmentosa: Up-to-Date. *Curr Genomics*. 2011 Jun;12(4).
17. Garip G, Kamal A. Systematic review and meta-synthesis of coping with retinitis pigmentosa: implications for improving quality of life. *BMC Ophthalmology* (2019) 19.
18. Pierret J. The illness experience: state of knowledge and perspectives for research. *Sociol Health Illn*. 2003; 25.

19. Greenhalgh T. Cultural contexts of health: the use of narrative research in the health sector. Copenhagen: WHO Regional Office for Europe; 2016, Health Evidence Network (HEN) synthesis report 49. http://www.euro.who.int/__data/assets/pdf_file/0004/317623/HEN-synthesis-report-49.pdf, last accessed on March 23, 2021.
20. Nowaczyk MJ. Narrative medicine in clinical genetics practice. Am J Med Genet A. 2012 Aug;158A(8).
21. Ragusa L, Crinò A, Grugni G, Reale L, Fiorencis A, Licenziati MR. Caring and living with Prader-Willi syndrome in Italy: integrating children, adults and parents' experiences through a multicenter narrative medicine research. BMJ Open 2020;10.
22. Marini MG. Narrative Medicine: Bridging the Gap between Evidence-based Care and Medical Humanities. London: Springer International Publishing 2016.
23. Kleinman A. The Illness Narrative, Suffering and Healing the Human Condition. New York: Basic Book 1989.
24. Greenhalgh T, Hurwitz B. Why study narrative? *BMJ* 1999; 318.
25. Marini MG, Languages of Care in Narrative Medicine. Words, Space and Time in the Healthcare Ecosystem. London: Springer International Publishing 2019.
26. Fioretti C, Mazzocco K, Riva S, Oliveri S, Masiero M, Pravettoni G. Research studies on patients' illness experience using the Narrative Medicine approach: a systematic review. *BMJ Open* 2016; 6.
27. Simonelli F, Sodi A, Falsini B, et al. Care pathway of RPE65-related inherited retinal disorders from early symptoms to genetic counseling: a multicenter Narrative Medicine project in Italy. *Clinical Ophthalmology*. In Press, 2021.
28. Audo I, Williamson N, Bradley H, Barclay M, Sims J, Arbuckle R, et al. Qualitative exploration of patient and caregiver experiences of visual function impairments and impacts on vision-dependent activities of daily living and health-related quality of life associated with Retinitis Pigmentosa and Leber Congenital Amaurosis in Germany and France. *Invest. Ophthalmol. Vis. Sci.* 2021;62(8):3585.
29. Kay C, Williamson N, Bradley H, Barclay M, Sims J, Arbuckle R, et al. Qualitative interviews with patients and caregivers regarding visual function impairments and impacts on vision-dependent activities of daily living and health-related quality of life in RPE65-related Retinitis Pigmentosa and Leber Congenital Amaurosis. *Invest. Ophthalmol. Vis. Sci.* 2021;62(8):3589.

30. Web Content Accessibility Guidelines (WCAG) 2.1. W3C Recommendations 05 June 2018. Available at https://www.w3.org/TR/WCAG21/, last accessed March 23, 2021.
31. Reid K, Soundy A. A qualitative study examining the illness narrative master plots of people with head and neck cancer. *Behav Sci* 2019; 9.
32. Peeters B, Marini M. Narrative medicine across languages and cultures: using minimal English for increased comparability of patients' narratives. In: Goddard C, ed. Minimal English for a Global World: Improved Communication Using Fewer Words. Basingstoke, UK: Palgrave Macmillan 2018: 259–86.
33. Charon R. The patient-physician relationship. Narrative Medicine: a model for empathy, reflection, profession, and trust. *JAMA* 2001; 286.
34. Banfi P, Cappuccio A, Latella ME, et al. Narrative medicine to improve the management and quality of life of patients with COPD: the first experience applying parallel chart in Italy. *Int J Chron Obstruct Pulmon Dis* 2018; 13.
35. Brédart A, Marrel A, Abetz-Webb L, Lasch K, Acquadro C. Interviewing to develop Patient-Reported Outcome (PRO) measures for clinical research: eliciting patients' experience. *Health Qual Life Outcomes*. 2014 Feb 5.
36. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation. Published on the Official Journal of the European Union L 119, May 4, 2016. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679, last accessed on March 23, 2021.
37. Personal data code protection. Legislat. Decree no. 196 of 30 June 2003. Published on the Italian Official Journal n. 174, July 29, 2003, Supplementary n. 123. https://www.camera.it/parlam/leggi/deleghe/Testi/03196dl.htm, last accessed on March 23, 2021.
38. Bazeley P, Jackson K. Qualitative Data Analysis with NVivo. London: SAGE 2013.
39. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. Qual Health Res. 2005 Nov;15(9):1277-88. doi: 10.1177/1049732305276687. PMID: 16204405.
40. Bury M. Illness narratives: fact or fiction? Sociology of Health and Illness. 2001;23(3).
41. Gibbs RW Jr. How metaphors shape the particularities of illness and healing experiences. Transcult Psychiatry. 2020 Nov 18:1363461520965424.

42. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care*. 2007 Dec;19(6).
43. Goffman E. Stigma. London: Penguin, 1963.
44. Spiegel T, De Bel V, Steverink N. Keeping up appearances: the role of identity concealment in the workplace among adults with degenerative eye conditions and its relationship with wellbeing and career outcomes. Disabil Rehabil. 2016;38(7)
45. Prem Senthil M, Khadka J, Gilhotra JS, Simon S, Pesudovs K. Exploring the quality of life issues in people with retinal diseases: a qualitative study. J Patient Rep Outcomes. 2017;1(1).
46. Lorenz B, Tavares J, van den Born LI, Marques JP, Scholl HPN; EVICR.net Group. Current management of patients with RPE65 mutation-associated inherited retinal degenerations (IRDs) in Europe. Results of a multinational survey by the European Vision Institute Clinical Research Network EVICR.net. *Ophthalmic Res*. 2021 Mar 8.

Figure legend

Figure 1 – Kleinman's classification: distribution and quotes from narratives.

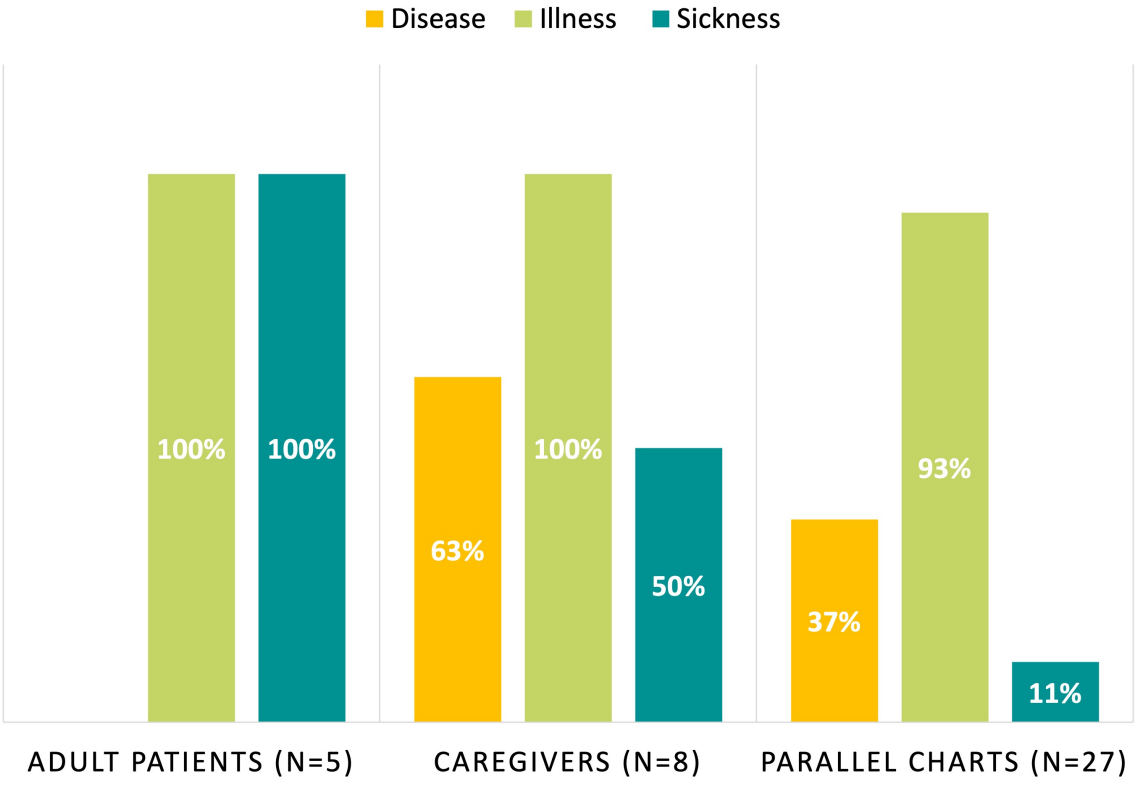
Figure 2 – Bury's classification: distribution and quotes from narratives.

Figure 3 – Metaphors used to describe RPE65-related IRDs: distribution and examples.

Figure 4 – Reported limitations in activities by patients and caregivers: essential data.

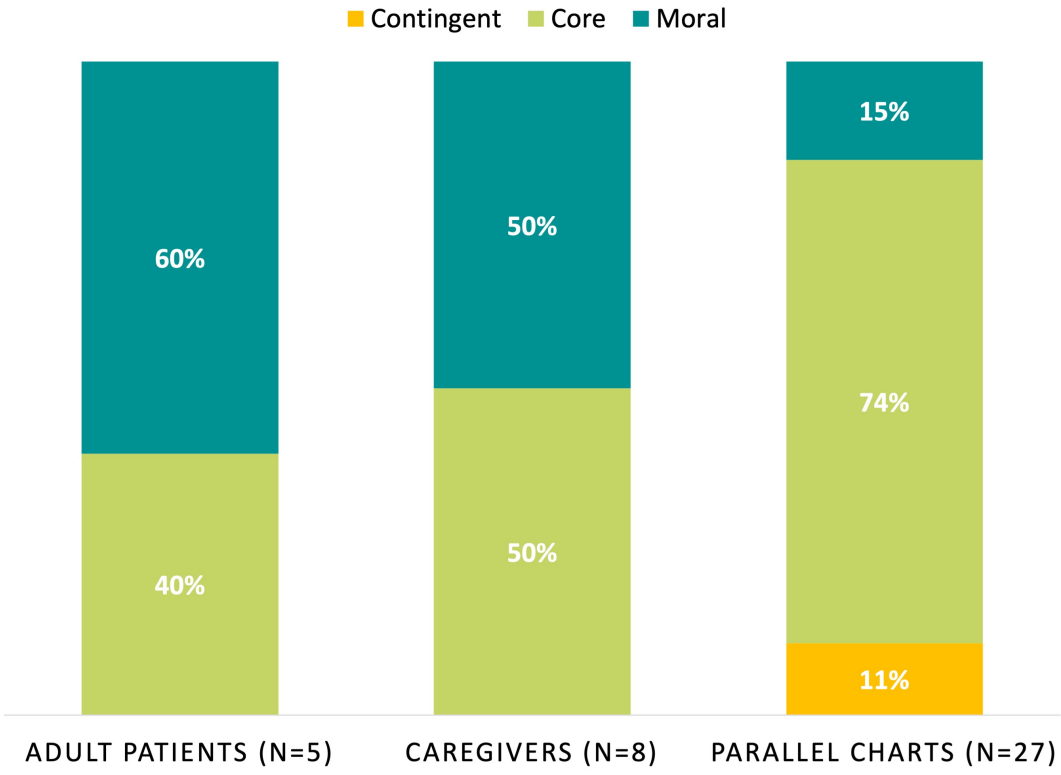
Figure 5 – Patients' QoL and RPE65-related IRDs overall interference on activities as perceived by patients and caregivers.

Figure 1 — Kleinman's classification: distribution and quotes from narratives



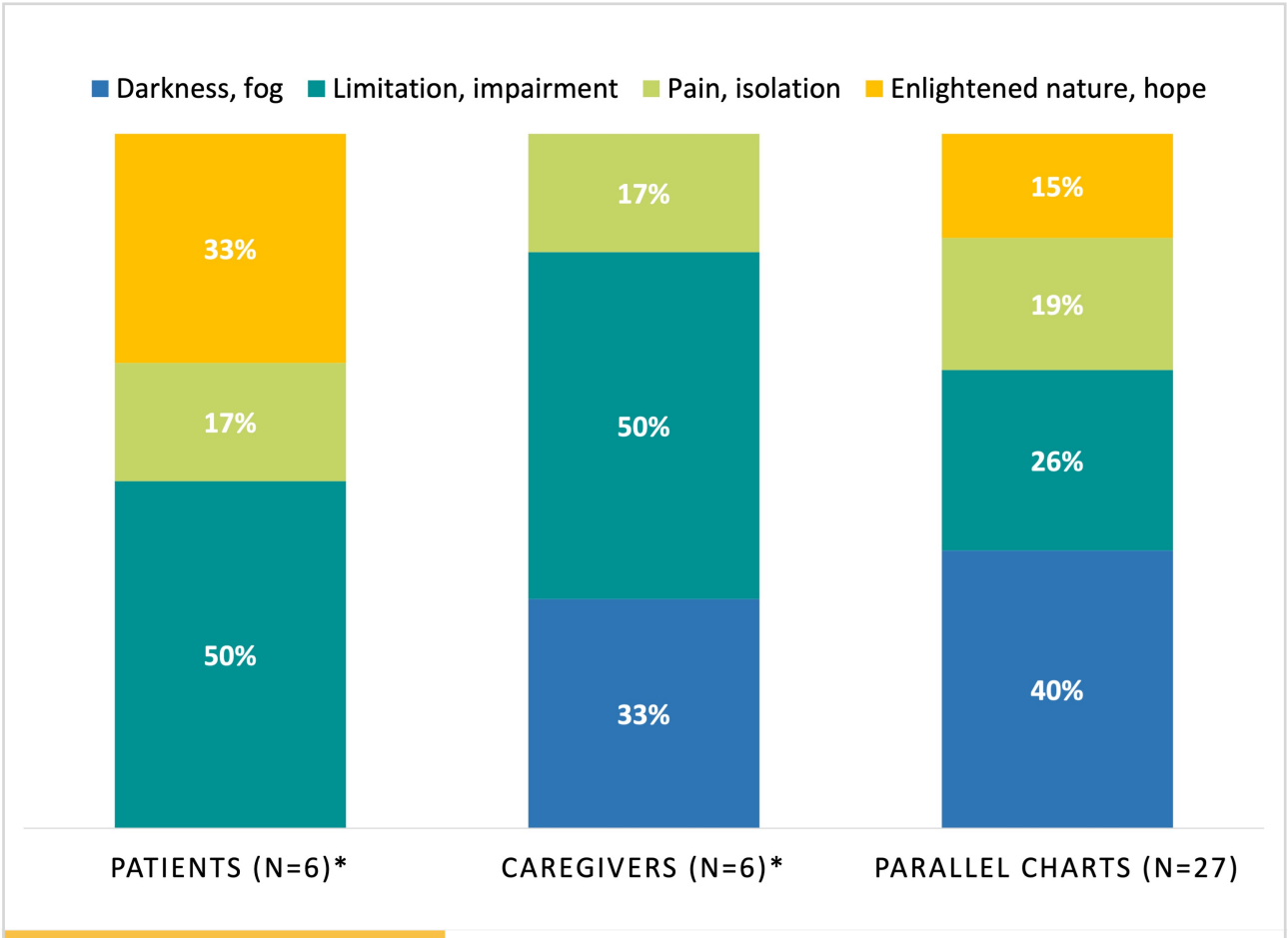
Disease	*—[...] All our research concentrated on what we observed, on the symptoms shown by our little girl: hyper fixation of light sources (light gazing), pressure on the eye sockets with the fingers (Franceschetti's oculo-digital sign), strabismus, failure to follow faces and objects, erratic movements of the pupils (nystagmus) and hypermetropia, which in ophthalmological medical literature led to a specific pathology*. (Caregiver 004) *—I thought he had Leber congenital amaurosis because of the head attitude and Franceschetti's oculo-digital sign together with nystagmus*. (Parallel chart 011)
Illness	*—I feel powerless because I cannot stop the progress of this disease. But at the same time, I feel serene because I have all the tools I need to cope with what will come. I feel melancholic because I know I will never again be able to do what I am doing today or what I did yesterday*. (Patient 004) *—When I was told it was an RPE65-related IRD, I felt empty inside, unable to realise the situation; I had never even heard of this condition*. (Caregiver 003) *—The child could not do many things and was fragile. I empathised with her parents' pain*. (Parallel chart 003)
Sickness	*—One afternoon, I was walking home with a friend and a classmate. We were chatting quietly when suddenly this boy introduced me to his grandmother as "the blind girl"*. (Patient 005) *—It was complicated to relate to other people and to make them understand the condition*. (Caregiver 006) *—Relationships with others are complex: relatives and friends instinctively protect these patients for fear that they might harm themselves*. (Parallel chart 019)

Figure 2 — Bury's classification: distribution and quotes from narratives



Contingent	*—I suspected the presence of retinal dystrophy. I went through the process of confirming my diagnostic suspicion*. (Parallel chart 009)
Core	*—Everything was unlocked when I realised that it was not difficult to ask for and accept help from others; that it wasn't so difficult to be different. Seeing – or rather, not seeing – was challenging to explain to others as long as it was difficult for me to accept*. (Patient 002) *—Today I feel calm. I have learned to accept this problem. I see that she gets by somehow; I always hope it doesn't get worse. I hope she has the opportunity to be treated because then she could be self-sufficient in doing things. I see her happy and hopeful*. (Caregiver 001) *—All patients always teach us something: paediatric patients often make us understand aspects of the disease that do not emerge with adults*. (Parallel chart 020)
Moral	*—Others say, judge, pity... Others are as unprepared for visual impairment as we are for death. The others are a disaster... A disaster to be reckoned with*. (Patient 001) *—I was angry, confused, incredulous. It's not fair. Why her? Why us?* (Caregiver 007) *—Sometimes I felt almost guilty for having healthy children. I looked at the parents – my peers – and saw their despair*. (Parallel chart 008)

Figure 3 - Metaphors used to describe RPE65-related IRDs: distribution and examples



Enlightened nature, hope	—*The world to me is a beautiful impressionist painting: as fascinating as it is imprecise... Shaded and inexact brushstrokes of colour... A world more imagined than seen, and yet, I would want to miss this painting for nothing in the world*. (Patient 001) —*A sun hidden in the clouds*. (Parallel chart 018)
Darkness, fog	—*This condition is like a thick, ever-present fog... it takes away your light, colours, and tiny details*. (Caregiver 005) —*A dark veil is dropped in front of his eyes and does not allow him to see the world as it should be seen but through a barrier*. (Parallel chart 005)
Limitation, impairment	—*Having this disease is like being a bird with only one wing. You only fly with the help of someone else*. (Patient 002) —*A horse with blinkers that cannot see to the sides*. (Caregiver 002) —*A bird in a cage*. (Parallel chart 025)
Pain, isolation	—*An eye with a monster eating it*. (Patient 005) —*A tear that runs down my child's face from her eyes; it runs long and doesn't stop...* (Caregiver 007) —*A child playing alone*. (Parallel chart 016)

*Non-responses = 2

Figure 4 - Reported limitations in activities by patients and caregivers: essential data

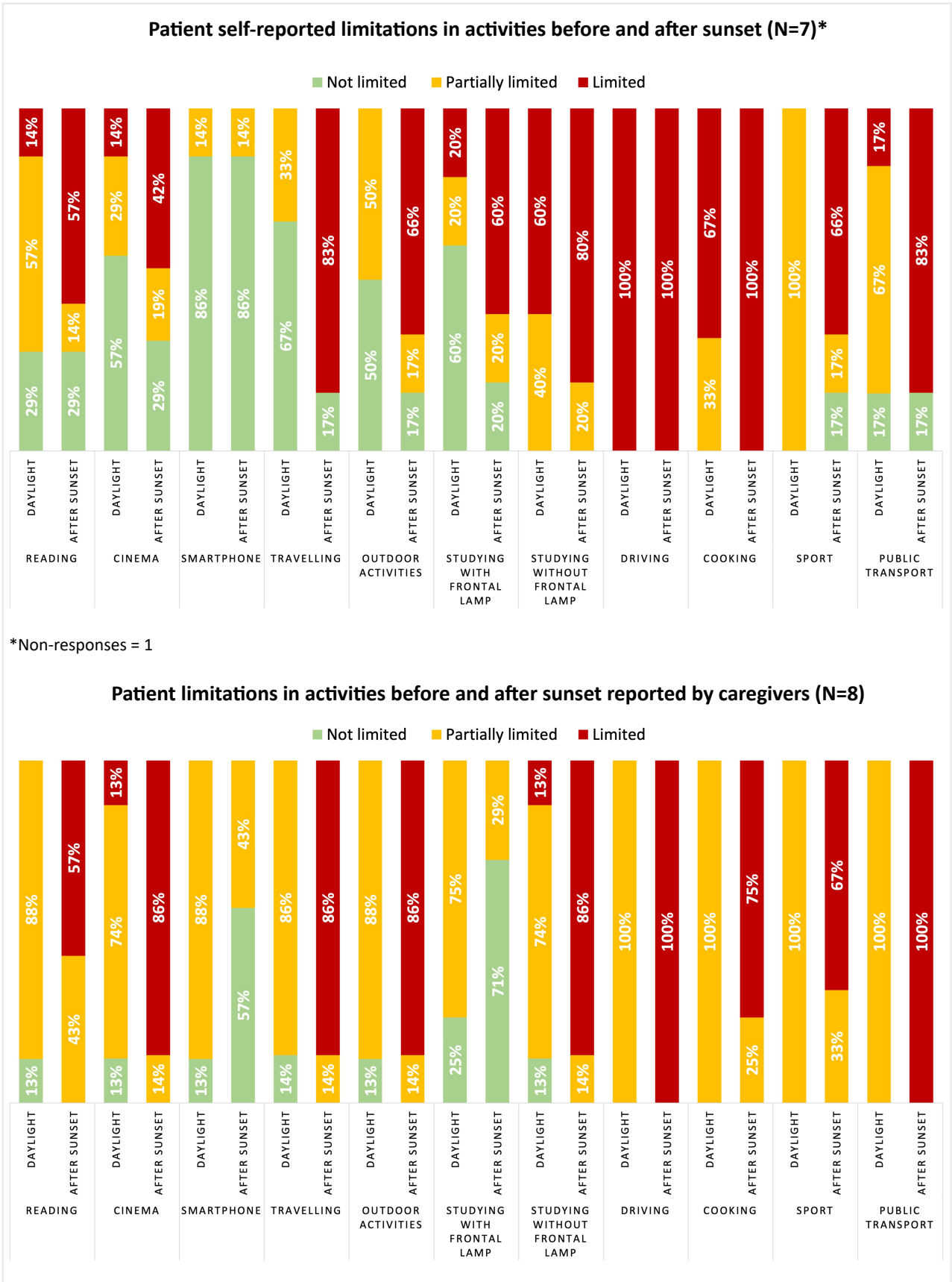
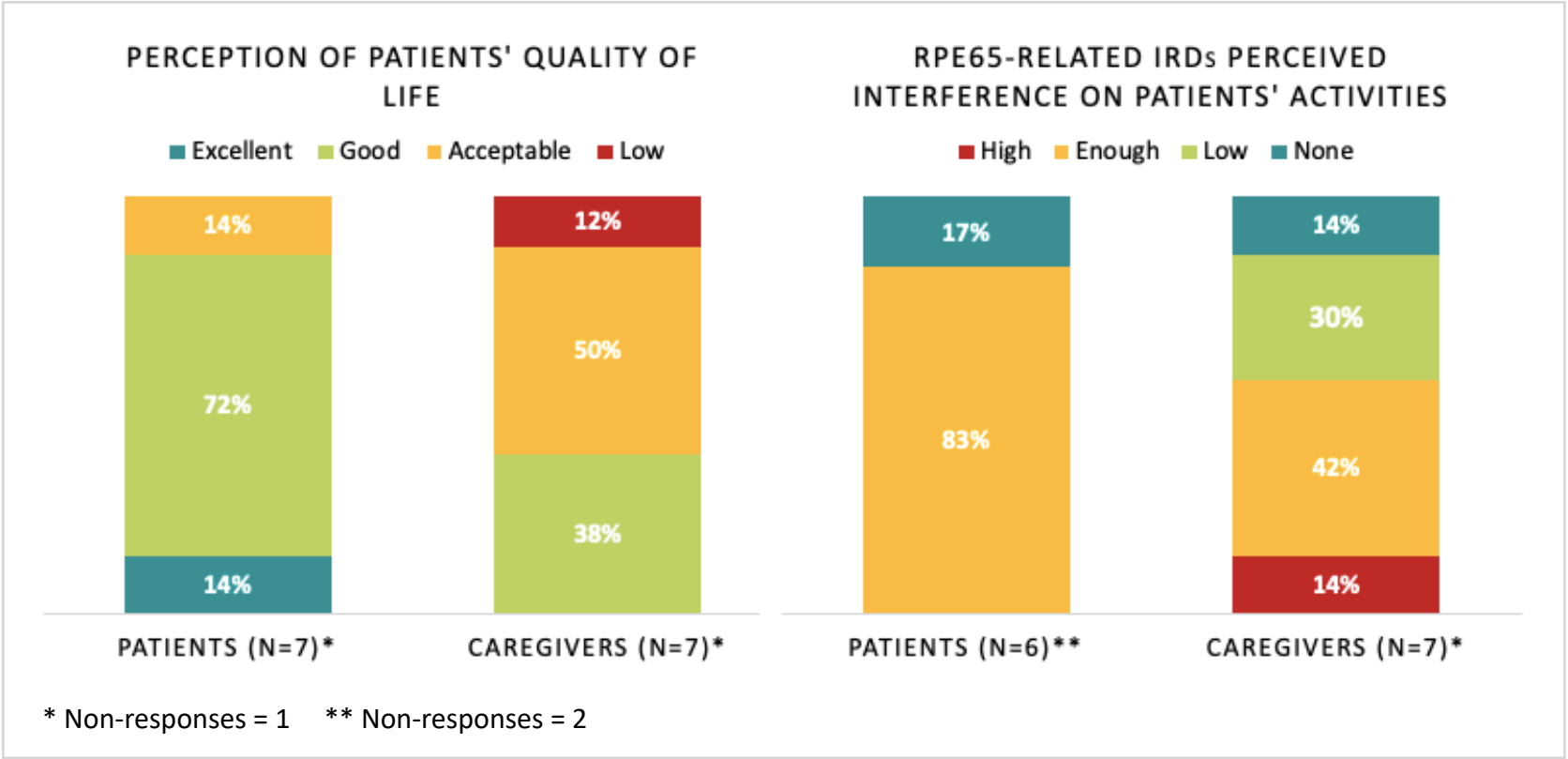


Figure 5 - Patients' QoL and RPE65-related IRDs overall interference on activities as perceived by patients and caregivers



* Non-responses = 1 ** Non-responses = 2

Supplementary file 1

Eye clinics specialised in Inherited Retinal Disorders (IRDs) involved in the BIRDS project

1. CRR Hereditary Retinal Degeneration, Careggi University Hospital – Florence, Italy
2. Paediatric Ophthalmology Unit, Children's Hospital A. Meyer – Florence, Italy
3. Department of Ophthalmology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore – Rome, Italy
4. Ophthalmology Department, Bambino Gesù IRCCS Paediatric Hospital – Rome, Italy
5. Multidisciplinary Department of Medical Surgical and Dental Specialties, Luigi Vanvitelli University Hospital – Naples, Italy

Supplementary file 2 – Illness plots and parallel chart

2.1. Illness plot addressed to patients

We invite you to tell us about your experience of living with a hereditary retinal disorder related to the RPE65 gene (RPE65-related IRD). You can write instinctively and freely, regardless of the form and length of your narrative. Any episode you consider significant will be welcome.

Before the IRD clinical diagnosis… The first signs that something was wrong… I felt… To understand what it was about… The facilities I visited, the healthcare professionals I met… Waiting for the clinical diagnosis… When they told me that it was an IRD, I felt... The genetic test for me was... That time, with family... With others... For me, seeing was... The activities I liked to do... The activities I could not do... At school/work... Healthcare professionals and treatments were... The centre where I am treated… Healthcare professionals and treatments are… Gene therapy for me is… Between one visit and the next… With my family… With other people… For me, seeing is… The activities I like to do… The activities I cannot do… Today at school/work… Rethinking about my care pathway, I would have liked that… Thinking about tomorrow, I feel… For tomorrow, I would like to…

Thank you for your time, energy and attention. We ask you one last question: How did you feel about writing your experience?

2.2. Illness plot addressed to caregivers of patients with an RPE65-related IRD

We invite you to tell us about your experience of living next to a person with a hereditary retinal disorder related to the RPE65 gene (RPE65-related IRD). You can write instinctively and freely, regardless of the form and length of your narrative. Any episode you consider significant will be welcome.

Before the diagnosis of IRD... When we first noticed that something was wrong... I felt... She/he felt... To find out what it was... Looking at her/him I thought... The facilities we visited, the healthcare professionals we met... Before the IRD clinical diagnosis... When we were told that it was an IRD, I felt... For me, the genetic test was... At that time, she/he with the family... She/he with other people... For her/him, seeing was... The activities she/he liked to do... The activities she/he could not do... At school/work... For her/him, I wanted... Healthcare professionals and treatments were... Today I feel... Today she/he feels... The IRD is... The centre where she/he is treated... Treatments and caregivers are... Gene therapy for me is... Between one visit and the next… With family... With other people… For her/him, seeing is... The activities she/he likes to do... The activities she/he cannot do... Rethinking to the care pathway, I would have liked that... Thinking about tomorrow, I feel... For tomorrow, I would like to...

Thank you for your time, energy and attention. We ask you one last question: How did you feel about writing your experience?

2.3. Parallel chart on patients affected by an RPE65-related IRD addressed to healthcare professionals

The first time I saw this person with an IRD, I thought… The patient and her/his relatives told me... Addressing symptoms, they told me that she/he could do/not do... I felt… And I did... Waiting for the clinical diagnosis... When I had to communicate the clinical diagnosis... Proposing the genetic test was... The relationships with family and other people of the person with IRD… For her/him, seeing was... Between one visit and the next… In her/his activities at work/study/play... Today this person... With family and other people... Today this person, during work/study/play… The people next to her/him... My goal for this patient is... With her/him I feel... From the relationship with the patient, I've learned... For tomorrow, I wish that I… For tomorrow I hope she/he...

Thank you for your time, energy and attention. We ask you one last question: How did you feel about writing your experience?

Supplementary file 3

3.1. Narrative from an underaged patient affected by an RPE65-related IRD

My mum realised that something was wrong when I was very young, about 18 months. I never felt different and was unaware of the difficulties. The professionals I met were helpful, kind, welcoming people who made me feel at home. While waiting for the diagnosis, I was very calm. When they told me that it was a hereditary retinal disease, nothing had changed for me. My eyes did not work as well as a healthy child's. The genetic test was a big step for me. The genetic test was just another test for me. At that time, we were very relaxed in my family. We had no particular problems with others. I've always seen that way. I don't know how others see. I like skating, dancing and cycling. At first, I could not ride a bike, then I did. I like school a lot, so I do not have any difficulties.
Some pills I will remember all my life because they were terrible, but the rest of the treatment was easy. Today I feel happy. The disease is stable for now, and I feel calm. I have more than one centre, and they are doing everything they can. The doctors are very nice and friendly, and I don't have any special treatment. Gene therapy is a great possibility for me because it will help keep my eyes stable, which would be very positive. Between one visit and the next, I feel calm and have no particular tension. I feel very relaxed with my family. With others, I am a sunny child. Seeing is a beautiful thing because it allows me to relate to the outside world. I like riding my bike, being with my animals, being with friends. I cannot do team sports. School is going well, and I feel at ease; I am learning to use the computer. Rethinking about the care pathway, I think everyone did what they could and what was right to do. When I think about tomorrow, I feel happy with the people who love me, and I would like everything to remain as it is now.

3.2. Narrative from an adult patient affected by an RPE65-related IRD

I don't remember a precise year, but the first signs that something was wrong were around the age of 6 or 7 when we were driving at night, and I realised that I couldn't see what my father needed to go. I could only see the light sources but not what they were illuminating. When I was 15 years old, I was driving back to the institute on Sunday afternoons; it got dark on the way, and I had a hard time walking from the station to the institute. If I had to walk together with other blind people, I would have done it with ease. I felt very uncomfortable, inappropriate, and inexplicably clumsy. In the evenings, I could not move to go out alone. If I accompanied other blind people, even two, I felt no discomfort, and the journeys went smoothly. I knew about my illness. I also met ophthalmologists who seemed to know less about it than I did. For the hope of treatment or recovery, ophthalmologists had already been consulted for my brother before I was born, or at least when I was small. While waiting for the diagnosis, I never had any expectations. When I learned that it was a hereditary disease, I was a child, and I had no reaction. I did the genetic test when I was 54 and, since I knew that there is a lot of retinitis, it was pure curiosity. Is it positive or negative to learn at 54 what exactly you have? Negative because it shows how much interest there is in such a disease: very little. It's good that research is going on, even if it's at a snail's pace. Only my mother has an attitude of some hope.

Having changed places I've gone to live [...] I have no way of comparing before and after. I never hid my problem, so they took me as I was. Seeing, even a little, even with difficulty, even when the amount of light allowed me to do things, "seeing" was, of course, more accessible. But since I knew that I would lose my sight sooner or later and that this took place over quite an extended period, I used these facts to run for cover, with the aim of not stopping. I liked cycling, which is different from riding a tandem bike, going out to look for glimpses of views, reading comics. The reading in black and the cycle rides gradually faded away. At school: I couldn't see the blackboard and do my homework alone. At work, as a teacher, I couldn't fill in the register by myself.
I only went for specific treatments for retinitis, useless but specific.
Today I feel the same as I did before. The disease has degenerated almost to the end. Functionally I am blind. Every now and then, I play the lamppost game, trying to catch the light from the lampposts as we walk down the street... in the evening.
When I go to the centre, I spend no less than 4 hours there, and 2 of them are waiting. So far, the people working there feel welcoming and helpful. So far, I've only had check-ups. I see gene therapy as an attempt to maintain the current faculties of the retina. We are still far from hoping for any kind of recovery, let alone a recovery measurable in tenths. I don't know why I've only had one visit to date where this therapy was mentioned for the first time. My family and I are on the same wavelength at the moment. So the family attends events to support my needs as they arise. I go to the swimming pool to do water gymnastics, with the others from our sports club we organise dinners in the dark. I have weekly music rehearsals with a group where only I am blind, we go to play in clubs, I go to see sculpture exhibitions if it is allowed to touch, of course. With my wife, who is also blind, we travel: when I have the chance, I like to get to know the cities, walking in their historical centres, alone. I read and listen to music. Unfortunately, I like to eat, so every opportunity is good to try a new restaurant. In everyday life, I am autonomous. Since there are many things I can do as a blind person, it seems useless to me to try at all costs to do something where sight is the only possibility. Like, for example: driving. I am autonomous in my activities; I only find difficulties when the computer aids are not adequate or modify the websites without considering the rules needed to include visually impaired users. I have been using personal assistants selected and trained by me for years in those areas where only sight works. Thinking back to my own care path, I would have liked to have had this care in the 1960s. My future is not conditioned by the presence of this care. But it seems worthwhile to me to do it: what will be, will be. We visually impaired people need civilisation. If in the behaviour of citizens, people, institutions, the observance of rules also prevails in the realisation of public and social things, we are in the right place. But in our society, this does not happen to a sufficient extent, so tomorrow will still be about making do as one can, with or without this care.

3.3. Narrative from a caregiver of a patient affected by an RPE65-related IRD

We toured the hospitals in our region. Visit after visit, the anamnesis and electrophysiological examinations were not sufficient for a diagnosis. Many signs and symptoms were confused between the different diseases affecting the retina. At six months, we realised that something was wrong with the involuntary eye movement, always searching for light, the lack of eye contact between

mother and child during breastfeeding. I felt an immense sense of absolute helplessness as a parent in front of her baby. I really needed to understand why... He is a very peaceful child; he plays, jumps, learns something new every day and knows how to give so much love. To understand what it was all about, we researched the subject because it helps us accept. I would see him and think that it's just a bad dream, with the hope of waking up to normality. We met very helpful and wonderful people.

When they told us that we needed to take a genetic test, I thought that there were no relatives with severe vision problems; it seemed so absurd. The genetic test was a simple saliva sample that allowed for greater accuracy; the genetic diagnosis was essential to know the gene that causes the disease. The wait for the diagnosis seemed like an eternity. The diagnosis, when it came, was a starting point; news like that turns your life upside down. He is a very calm child and learns every day to become more and more autonomous. When they told us that it was a hereditary retinal disease, I felt terrible because you don't expect it. It seems impossible to me to have a congenital disorder of a genetic nature in a family where there were no known cases. At that time, the environment was fundamental because I was more autonomous. At home, with the organisation of spaces, he moves on his own, and so he gets used to making do. He is friendly and loves being with other kids; he is cheerful, curious, and intelligent. There is a difference between seeing the light and not seeing it at all, so we are confident that everything has not degenerated. He likes to do everything, watch cartoons and knows some dialogues by heart. Among the activities he finds hard to do are playing football, drawing, playing basketball. As a parent, the only thing you want in life is to protect your children. It is challenging to live with this disease because I have mortifications in every area of life. We are waiting for the gene therapy to finally allow us to see the light at the end of the tunnel.

Today I feel very serene, and I never stop dreaming that after the discovery, the waiting, the hope, the light will finally come. Today he feels more peaceful, and day after day, he learns to be more vital to face his life. The disease is genetic, rare, incurable; we are healthy carriers of the defect and have passed it on to our son. The hospital that is treating us is a centre of excellence, and we have carried out the genetic test. Getting a diagnosis for a rare disease is not always easy. It is a long and tiring process. The time between checks is too long. For me, gene therapy would be the miracle we have been waiting for, as we are entering an era where diseases that were once incurable are becoming curable. Thanks to the love of those around him, he is learning to live with all the strength he needs. He is an adorable child and knows how to make others love him. He is a very healthy child who rarely gets sick. His eyesight is not yet very impaired; otherwise, he is very cheerful. Rethinking the care pathway, I would have liked to have had more information on this disease's knowledge, together with the proper psychological and educational support. If I had to imagine a service for all the people with the same disease as my son, I would think of a specialised centre for this disease, which could guarantee proper support for parents who face enormous difficulties. When I think of tomorrow, I don't know what awaits us. Still, we are very enthusiastic about the progress of science. I would like to see proper care centres and improved schooling for people with this disease in the future. Reading difficulties are essential, and there is a lack of adequate tools to deal with them.

3.4. Parallel chart on a patient affected by an RPE65-related IRD from a healthcare professional

Poor child: he is not living his life like his other healthy peers. The parents reported that they needed advice on how to make him as autonomous as possible. He could not play, run, be independent in his personal and school affairs. He could not orientate himself in space. The situation worsened from sunset onwards when the child panicked. The whole family hardly ever went out in the evening, not even for a simple dinner. I felt obliged to build a personalised rehabilitation programme to find alternative strategies to give the family tools and reassure the child to increase his self-esteem. I asked the child to tell me everything he wanted to do, everything he thought to do poorly, and his fears when he got stuck on various occasions. I asked the parents what they saw when they were with their child, their fears, their difficulties, what they wanted help with, what they hoped for. I gradually started to indicate how to organise the house according to the child's size, what light or contrast measures should be taken and how to organise the school material to make it more usable. It was not my job to communicate the diagnosis.

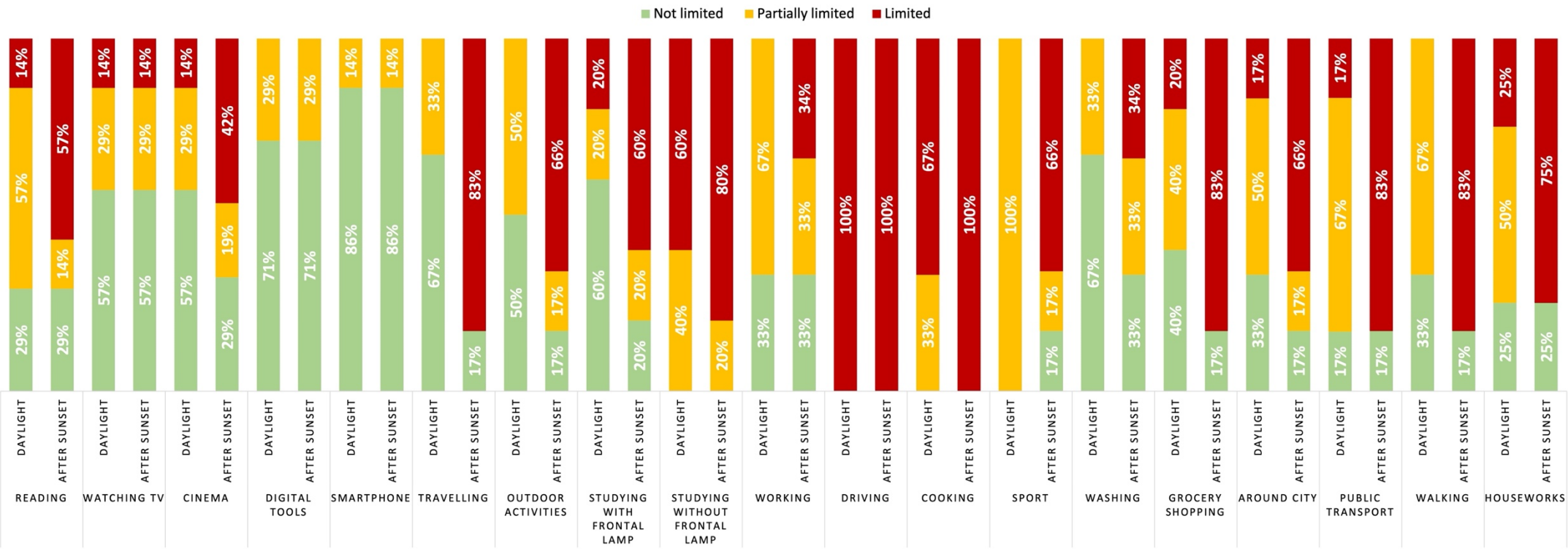
Other people often do not understand what and how he sees, so it ranges from denial to being overprotective. To see was not to fall, not to stumble, play football, watch television together with the family, write in the notebook without difficulty, and read without difficulty. The family was heartened and happy about the small degree of autonomy their child was able to achieve. The child began to experiment on his own without requiring the constant presence of others. When studying, the child felt frustrated because he realised that he could not write or read like the others. He felt different because he could not demonstrate his abilities and was frustrated because he could not keep up with others.

Today, he is more confident about himself, his abilities and also his limits. He has learned to set himself small goals, overcome them with his own alternative strategies and move forward. With other people, he is more present and less dependent. At school, he has found his own alternative methods to do almost the same as other peers; he participates more in the class group and verbalises his visual difficulties when he has a problem. The people around him seem more serene and confident in his potential. My aim is to make him aware of his challenges to face them with alternative strategies and overcome them even if with limitations. I feel stimulated to find with him alternative solutions to make him autonomous. I am learning from the caring relationship that there is no limit to the potential.

I would like to be able to help them even more in the future. I would like him to be aware of how extraordinary his will power is.

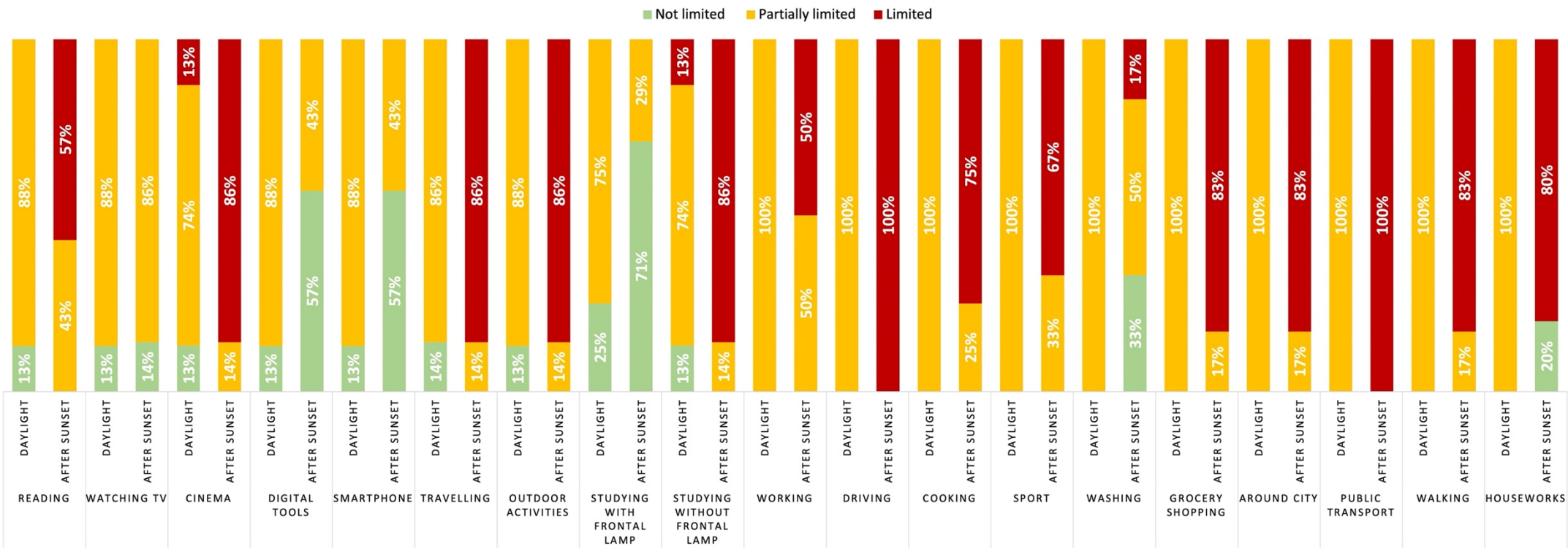
Supplementary file 4 – Reported limitations in activities by patients and caregivers

4.1. Patient self-reported limitations in activities before and after sunset (N=7*)



*Non-responses: 1.

4.2. Patient limitations in activities before and after sunset reported by caregivers (N=8)



Standards for Reporting Qualitative Research (SRQR)*

http://www.equator-network.org/reporting-guidelines/srqr/

	Page/line no(s).
Title and abstract	
Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	p. 1, ll. 1-3
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	p. 2, ll. 34-56
Introduction	
Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	pp. 3-4, ll. 64-91
Purpose or research question - Purpose of the study and specific objectives or questions	p. 4, ll. 92-101
Methods	
Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	p. 4, ll. 85-96
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	p. 6, ll. 144-145
Context - Setting/site and salient contextual factors; rationale**	p. 5, ll. 109-118
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	p. 5, ll. 119-122
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	p. 6-7, ll. 150-158
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	pp. 5-6, ll. 123-145

Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	pp. 5-6, ll. 123-145
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	pp. 8, ll. 183-188
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	pp. 7-8, ll. 159-181
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	pp. 7-8, ll. 159-181
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	//

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	pp. 7-16, ll. 169-300
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	pp. 7-16, ll. 169-300

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	pp. 17-20, ll. 316-392
Limitations - Trustworthiness and limitations of findings	pp. 20-21, ll. 393-403

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	pp. 22, ll. 440-443
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	p. 22, ll. 444-445

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014
DOI: 10.1097/ACM.0000000000000388