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Fit for Purpose PROMs for IRDs and Dry AMD

Ocular Disease Forum 1

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Disclosures

No disclosures to report

Outline

Introduction

Measurement for IRDs and AMD

- Many existing PROMs are not fit for purpose
- Alternatives

Gaps and Open Questions

Introduction: PROMs and What They're Used For

What are PROMs?

Instruments or tools designed to capture the "status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" (US FDA 2009).

May measure a single concept (e.g., pain intensity) or multiple concepts (severity of visual symptoms; limitations of activities of daily living; HRQOL)

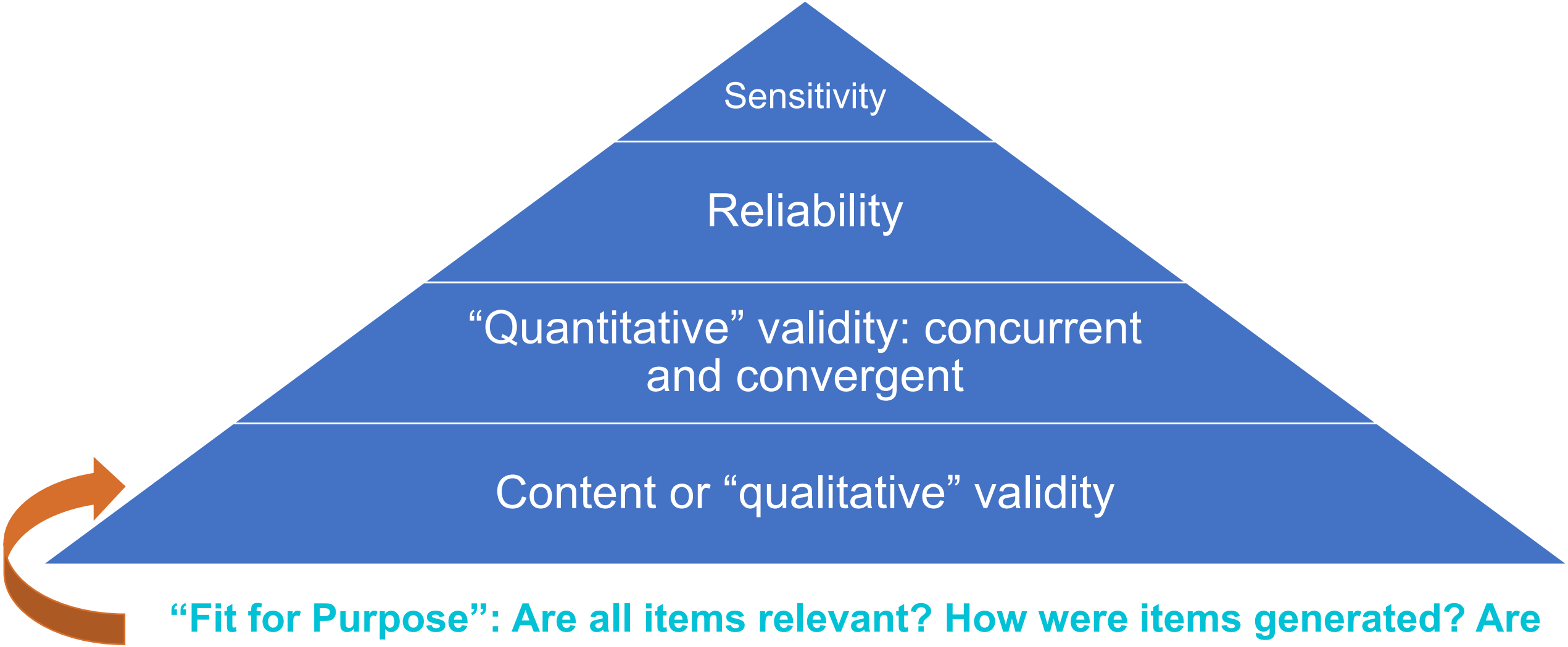
What are they used for?

Demonstrating benefits or harms of treatments and health technology assessments (particularly measures that can be converted to health utility scores)

Introduction: Early Milestones

Year	Milestone	Comment
1977	First publication for an RP-specific PROM, the Field Expander Questionnaire (Kennedy et al. 1977)	Evaluate experience with a field expander device
1998	MDQ (Geruschat et al. 1998)	Perceptions of difficulties with mobility
	ADVQ (Szlyk et al. 1998)	Functioning on everyday tasks in RP patients (6 domains)
	NEI-VFQ (Mangione et al. 1998)	Vision-targeted health-related quality of life (HRQOL); 51 items; no IRD patients involved in concept elicitation
2001	NEI-VFQ short form (Mangione et al. 2001)	25 items
2009	"Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" (US FDA 2009)	Describes how the FDA will review PROMs when they are the basis for label claims.

Introduction: Evaluation of PROMs for their Intended Use (FDA 2009)



“Fit for Purpose”: Are all items relevant? How were items generated? Are they understood? How do the items and concepts relate to each other?

Case 1: Is the NEI-VFQ a Good Fit for *RLBP1*-Associated RP?

Methods

- Recruited 21 patients (including 1 child) in Canada and Sweden with *RLBP1*-associated RP
- Conducted semi-structured concept elicitation interviews and cognitive debriefing of the NEI-VFQ, Low Luminance Questionnaire (LLQ), and four items on the Visual Activities Questionnaire (VAQ)
- Interviewed three expert clinicians
- Analyzed verbatim transcripts

Patient Characteristics

- *RLBP1*-RP is characterized by severe night blindness early in life, progressive visual field constriction, and decreasing central VA in early adulthood.
- Age, mean (range) = 45 (11-67)
- 14/21 had visual acuity categorized (WHO classification) as severe or very severe [20/200 or worse]
- 19/21 had visual field categorized (WHO classification) as severe or very severe
- 14/21 had both visual acuity and visual field categorized as severe or very severe
- Years from symptoms to diagnosis, mean (range) = 14 years (1-62)

Case 1: Conceptual Model for *RLBP1*-Associated RP

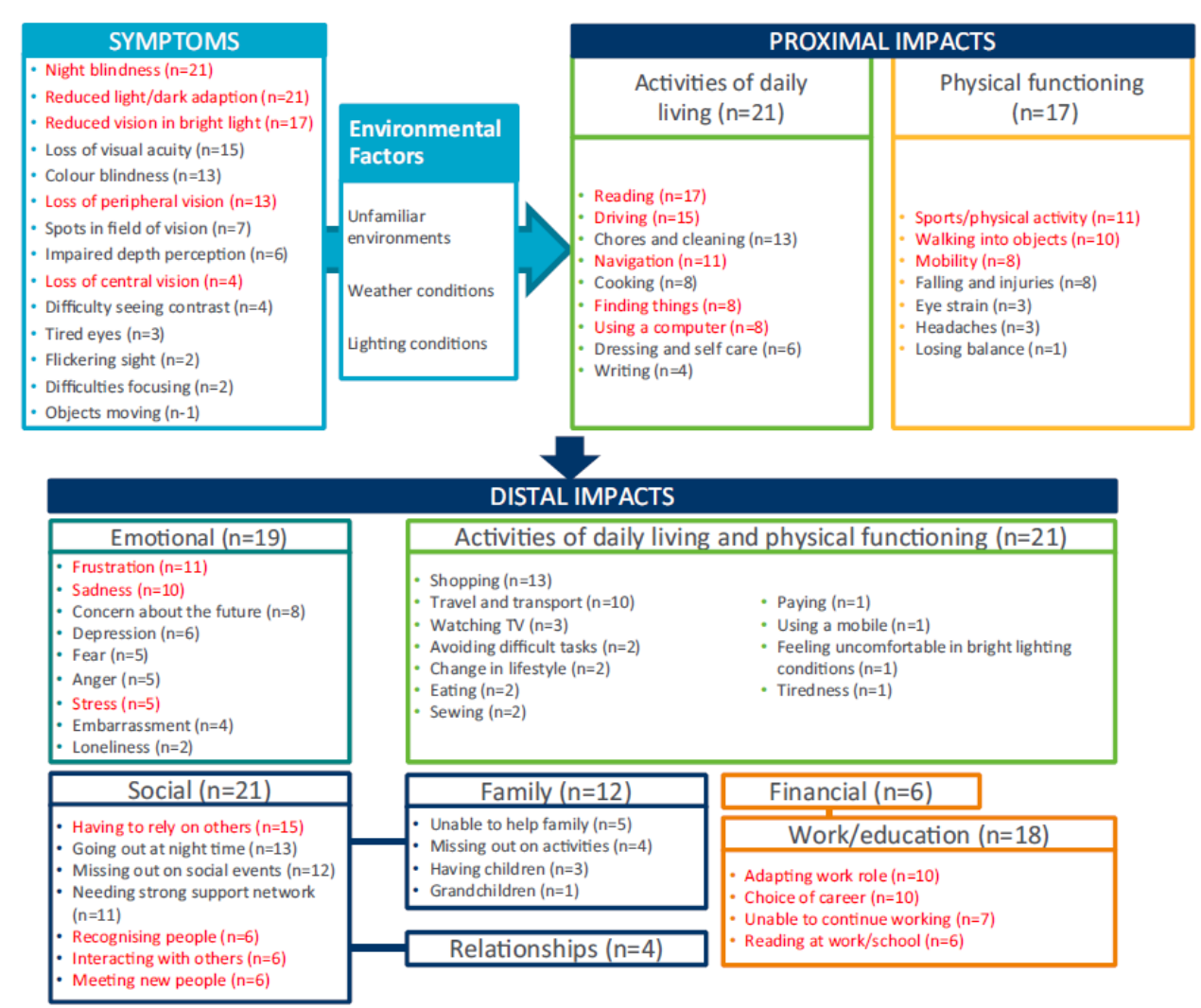


Fig. 1 Conceptual model for *RLBP1* RP. Concepts in red were considered 'key concepts' by expert clinicians

Image (unmodified) from:
Green J, Tolley C, Bentley S, Arbuckle R, Burstedt M, Whelan J, Holopigian K, Stasi K, Sloesen B, Spera C, Deslandes JY, Mullins A. Qualitative Interviews to Better Understand the Patient Experience and Evaluate Patient-Reported Outcomes (PRO) in RLBP1 Retinitis Pigmentosa (RLBP1 RP). Adv Ther. 2020 Jun;37(6):2884-2901. doi: 10.1007/s12325-020-01275-4. Epub 2020 May 5. PMID: 32372289; PMCID: PMC7467452.

Case 1: Symptoms and Proximal Impacts of Conceptual Model for *RLBP1*-Associated RP

Symptoms

- Night blindness (n=21)
- Reduced night / dark adaptation (n=21)
- Reduced vision in bright light (n=17)
- Loss of visual acuity (n=15)
- Colour blindness (n=13)
- Loss of peripheral vision (n=13)
- Spots in field of vision (n=7)
- Impaired depth perception (n=6)
- Impaired central vision (n=4)
- Difficulty seeing contrast (n=4)
- Tired eyes (n=3)
- Flickering sight (n=2)
- Difficulties focusing (n=2)
- Objects moving (n=1)

Environmental Factors

Unfamiliar environments

Weather conditions

Lighting conditions

Activities of Daily Living

- Reading (n=17)
- Driving (n=15)
- Chores and cleaning (n=13)
- Navigation (n=11)
- Cooking (n=8)
- Finding things (n=8)
- Using a computer (n=8)
- Dressing and self care (n=6)
- Writing (n=4)

Physical Functioning

- Sports / physical activity (n=11)
- Walking into objects (n=10)
- Mobility (n=8)
- Falling and injuries (n=8)
- Eye strain (n=3)
- Headaches (n=3)
- Losing balance (n=1)

Case 1: No, the NEI-VFQ is not a Good Fit for *RLBP1*-Associated RP

Table 4 Summary of conceptual coverage of instruments

	Concept	VFQ-25	LLQ	VAQ
Symptoms	Night blindness	✓ (2)	✓ (11)	X
	Light/dark adaptation	X	X	✓ (4)
	Vision in bright light	X	✓ (3)	X
	Visual acuity	✓ (3)	✓ (4)	X
	Color blindness	✓ (1)	✓ (1)	X
	Loss of peripheral vision	✓ (1)	✓ (3)	X
	Spots in field of vision	X	X	X
	Depth perception	X	✓ (2)	X
	Seeing contrast	X	✓ (2)	X
	Tired eyes	X	X	X
	Flickering sight	X	X	X
	Difficulties focusing	X	X	X
	Objects moving	X	X	X
Impact on ADLs - proximal	Reading	✓ (2)	✓ (5)	X
	Driving	✓ (6)	✓ (5)	X
	Chores and cleaning	✓ (1)	X	X
	Cooking	✓ (1)	X	X
	Finding things	✓ (1)	✓ (1)	X
	Using a computer	X	X	X
	Dressing and self-care	✓ (1)	X	X
	Writing	X	X	X
Impact on ADLs - distal	Shopping	X	X	X
	Navigation	X	X	X
	Travel and transport	X	X	X
	Watching TV	X	X	X
	Home	X	X	X
	Avoiding difficult tasks	X	X	X
	Eating	X	✓ (1)	X
	[illegible]	[illegible]	[illegible]	[illegible]

Concepts with a ✓ are assessed by the instrument; concepts with an X are not.

Image (cropped but otherwise unmodified) from:
Green J, Tolley C, Bentley S, Arbuckle R, Burstedt M, Whelan J, Holopigian K, Stasi K, Sloesen B, Spera C, Deslandes JY, Mullins A. Qualitative Interviews to Better Understand the Patient Experience and Evaluate Patient-Reported Outcomes (PRO) in RLBP1 Retinitis Pigmentosa (RLBP1 RP). Adv Ther. 2020 Jun;37(6):2884-2901. doi: 10.1007/s12325-020-01275-4. Epub 2020 May 5. PMID: 32372289; PMCID: PMC7467452.

Case 2: Is the VALVVFQ a Good Fit for *USH2A*-Associated Retinal Degenerations?

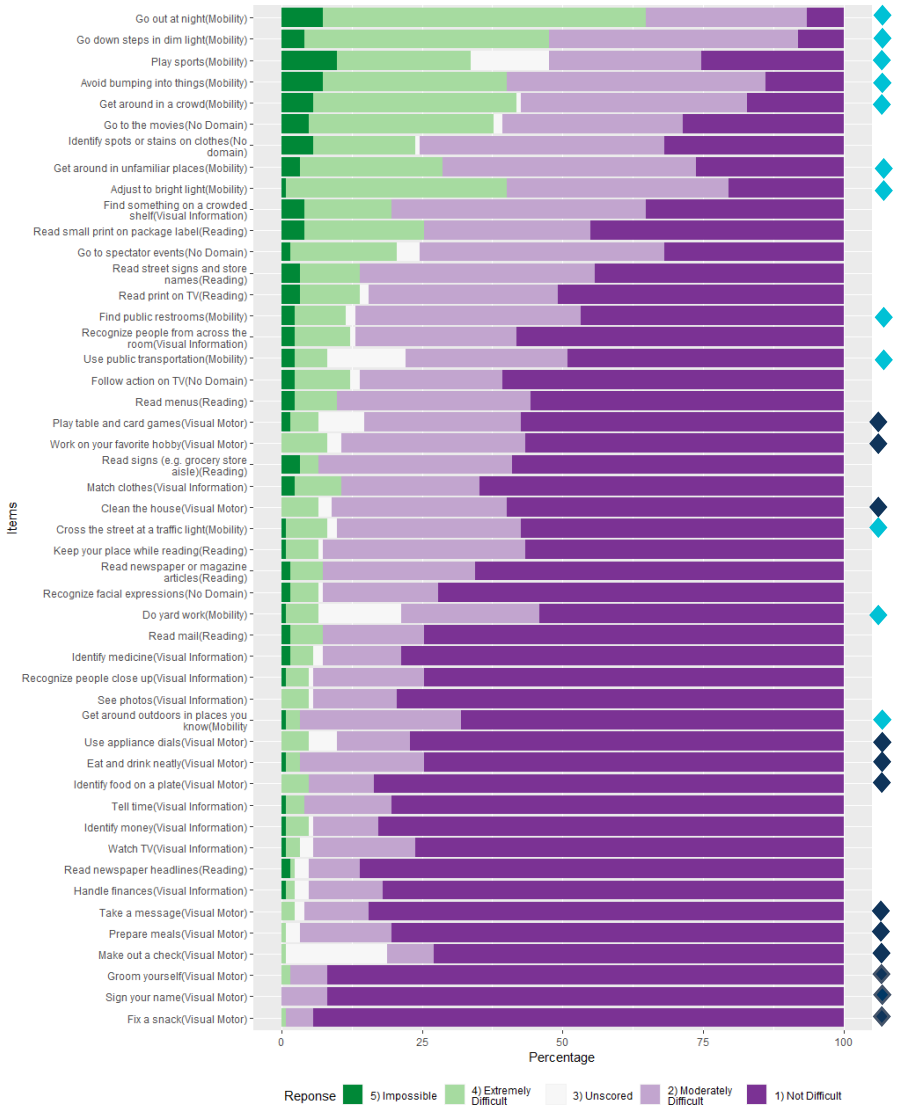
Methods

- Administered the 48-item Veteran Affairs Low-Vision Functioning Questionnaire (VALVVFQ-48) to 99 participants in the RUSH2A natural history study
- Used Rasch type scoring method to estimate:
  - Item difficulty score for each item (48)
  - Functional vision score for each person per domain
- Missing FV scores generated when all responses were 'Not Difficult' for items in particular domain: Mobility (0 missing); Reading (19 missing); Visual Information (26 missing); Visual Motor (35 missing)

Participant Characteristics (overall cohort)

- *USH2A*-associated retinal degenerations (autosomal RP and Usher syndrome Type 2) are characterized by loss of peripheral vision, preserved central acuity into adulthood
- Age, median (range) = 44 (24-75)
- Visual acuity study eye, median (range) = 80 ETDRS letters (18-94) [median equivalent to 20/50]
- Static perimetry total Hill of Vision, median (range) = 19.3 dB-sr (0.2-22.7) [well below normative value]
- Duration of disease, median (range) = 15.3 years (1-60.3)

Case 2: No, the VALVVFQ is a Poor Fit for *USH2A*-Associated Retinal Degenerations



Denotes items in “Mobility” domain

Examples:
- “Go out at night”
- “Go down steps in dim light”
- “Play sports”
- “Avoid bumping into things”

Denotes items in “Visual Motor” domain, most of which are too easy

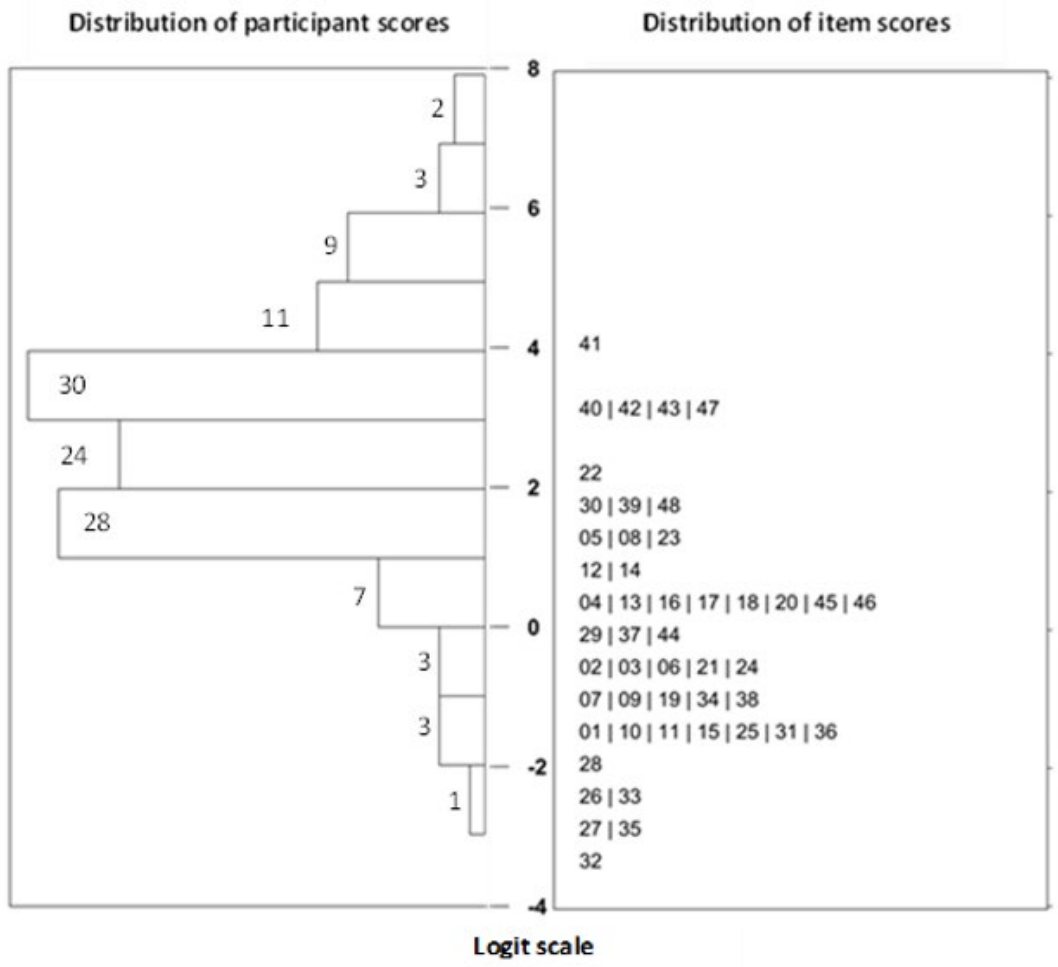
Examples:
- “Fix a snack”
- “Sign your name”
- “Groom yourself”
- “Make out a check”

Case 2: No, the VALVVFQ is a Poor Fit for *USH2A*-Associated Retinal Degenerations

There is not sufficient item coverage of individuals with better functional vision.

This “low vision” instrument is not well targeted to individuals with well preserved central vision.

Therefore, the overall score does not discriminate well between better vs. worse functional vision.



Better functional vision

Worse functional vision

Case 3: Is the NEI-VFQ a Good Fit for Dry AMD?

Methods

- Targeted literature review to document most important signs, symptoms, and impacts related to dry AMD
- Recruited 20 dry AMD patients in the United States and conducted concept elicitation interviews (to concept saturation)
- Interviewed 5 dry AMD clinicians about dry AMD symptoms and consequences on patients lives
- Developed a conceptual model from all sources

Participant (Patient) Characteristics

- Age, mean (range) = 69 (51-83)
- Disease severity: mild, moderate, severe = 5, 10, 5 participants
- Two eyes affected = 12 participants

Case 3: No, the NEI-VFQ is a Poor Fit for Dry AMD

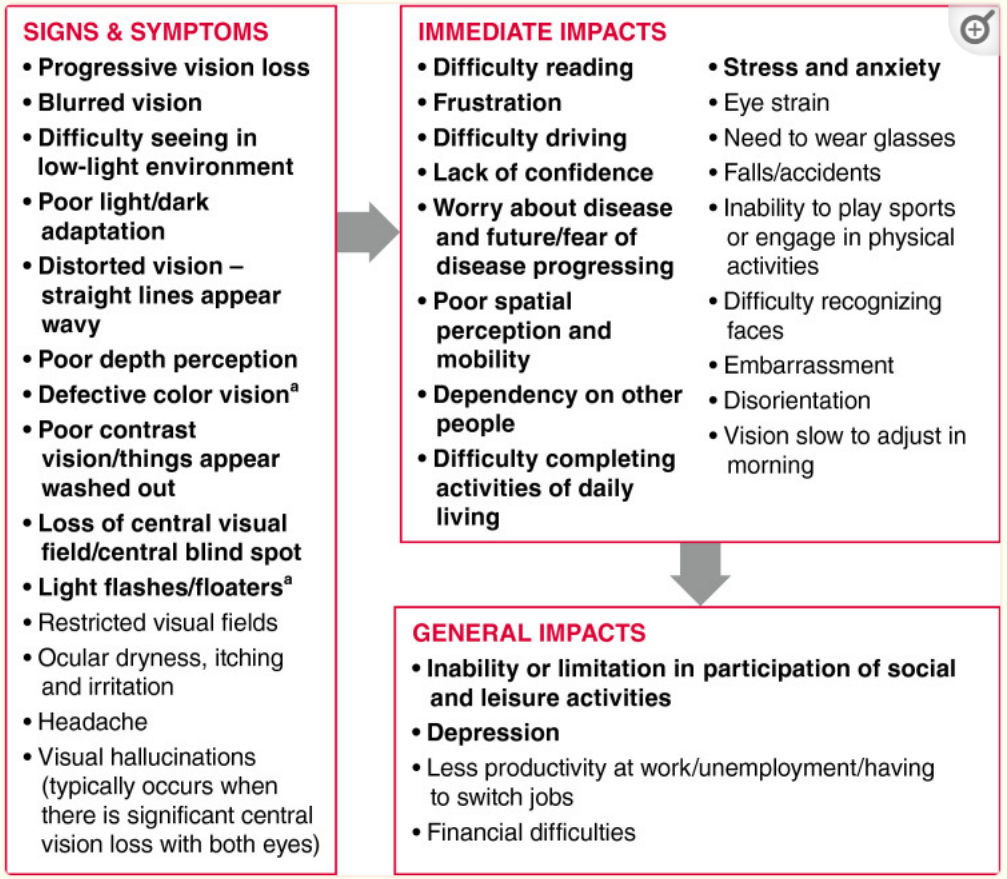


Fig. 4

Final dry AMD conceptual model. Bold text: Salient symptoms/impacts were defined as those which were mentioned by ≥ 50% of patients and received a disturbance rating of ≥ 5 on average. *AMD* age-related macular degeneration. [a]Concepts outside the saliency definition, but included due to proximity of mentions and disturbance to the salient concepts

No disease-specific instruments have been developed for dry AMD.

The NEI-VFQ does not include most of the predominant ("salient") signs and symptoms of dry AMD.

Michigan Retinal Degeneration Questionnaire (MRDQ) Has Been Developed For IRDs

- Developed for adults with variety of IRDs (rod-cone, cone/cone-rod, macular) following contemporary guidance and psychometric methods
- **59 items across 7 visual domains** (central vision, color vision, contrast sensitivity, scotopic vision, photopic peripheral vision, mesopic peripheral vision, photosensitivity)
- **Assesses difficulties with tasks and accommodations**
  - Difficulty reading books, magazines, or mail?
  - Use someone's arm to walk during the night?
  - Touch things around you to move during the day?
- **Measurement properties**
  - Psychometrically validated (understood by respondents)
  - Construct validity
  - Reliable

Lacy et al, 2020; Lacy et al, 2021

ViSIO-PRO (adults) and ViSIO-ObsRO (children) Have Been Developed for RP / LCA

- Developed for individuals with variety of genetic causes of RP / LCA
- Incorporates mediating factors of available lighting and familiarity of environment (recall the conceptual framework from *RLBP1)*.
- **Activities and other impacts**
  - PRO: “In the past 7 days, how often have you felt frustrated because of your vision?”
  - ObsRO: “In the past 7 days, have you seen your child have difficulty when going down steps, stairs, or stepping off a curb in good lighting without help from someone else because of their vision?”
- **Measurement properties**
  - Psychometrically validated (understood by respondents)
  - Construct validity, convergent validity (correlation with visual function)
  - Reliable

Kay et al. 2020, Kay et al 2021, Audo et al. 2022

Gaps and Open Questions

- There will never be a perfect, fit for purpose, PROM for every IRD (requires a lot of evidence).
- Practical recommendations for an informed “PROM strategy”:
  - Start with a thorough understanding of natural history, disease impacts, and likely benefits of a new therapy;
  - If not **well documented**, conduct qualitative research to determine most common or important symptoms and impacts;
  - Determine which disease impacts are most likely to be modified by the new treatment considering its mechanism;
  - Identify whether any existing PROM, or subset of items of a PROM, could address the anticipated benefits.
- How sensitive are the new PROMs to effects of treatment?
- Is it possible to develop a set of tools applicable across ophthalmology?
- What else do patients have to tell us about what’s important?

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