

Article title

Development of Clinician-Reported Outcome (ClinRO) and Patient-Reported Outcome (PRO) Measures for Eyebrow, Eyelash and Nail Assessment in Alopecia Areata

Journal

American Journal of Clinical Dermatology

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Funding sources

This study was funded by Eli Lilly and Company.

Disclosures of potential conflicts of interest

Helen Kitchen, Sarah Knight, Natalie V.J. Aldhouse, and Jake Macey are employees of DRG Abacus, a health economic and outcomes research consultancy that consults with various pharmaceutical companies. Kathleen W. Wyrwich was an employee and stockholder at Eli Lilly and Company when this research was conducted; she is now an employee and stockholder at Pfizer Inc. Fabio P. Nunes, and Yves Dutronc are employees and stockholders at Eli Lilly and Company. Dr. Brett King has served on advisory boards and is a consultant and clinical trial investigator for Eli Lilly and Company; he has served on advisory boards and/or is a consultant and/or is a clinical trial investigator for Aclaris Therapeutics Inc, Arena Pharmaceuticals, Bristol-Meyers Squibb, Concert Pharmaceuticals Inc, Dermavant Sciences Inc, and Pfizer Inc. Natasha Mesinkovska has no potential conflicts of interest. Eli Lilly and Company have commissioned DRG Abacus, Dr. Justin M. Ko and Dr. Brett A. King to consult on clinical outcomes assessment strategies for alopecia areata.

Online Resources/Supplementary Material

Development of ClinRO and PRO Measures for Eyebrow, Eyelash and Nail Assessment in Alopecia Areata
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Online Resource 1 Patient interview inclusion and exclusion criteria

Criteria	Included	Excluded
Demographics	<ul style="list-style-type: none"> Male or female <i>Round 1</i>: Age ≥ 12 years at time of consent <i>Round 2 & Photoguide interviews</i>: Age 18–60 years at time of consent 	<ul style="list-style-type: none"> Participated in any other round of this study <i>Photoguide interviews</i>: Has previously been a photograph subject for the photoguide
Diagnosis	<ul style="list-style-type: none"> <i>Round 1 & 2</i>: Severe AA diagnosed by a clinician and determined by SALT score $\geq 50\%$ <i>Round 1 & 2</i>: A history of AA episodes lasting >6 months but <8 years <i>Round 1</i>: Successful JAKi treatment but SALT score $\geq 50\%$ prior to treatment <i>Photoguide interviews</i>: Severe AA diagnosed by a clinician and determined by $\geq 50\%$ in the past 6 months (patient can have experienced growth and be at $\leq 50\%$ at the time of recruitment) <i>Photoguide interviews</i>: Patient has current or previous experience of at least some eyebrow or/and eyelash or/and nail involvement as part of their AA 	<ul style="list-style-type: none"> <i>Round 1</i>: Patients with known androgenic alopecia <i>Round 2 & Photoguide interviews</i>: Patients with other forms of alopecia, including male or female pattern hair loss
Comorbidities		<ul style="list-style-type: none"> Active psoriasis, atopic dermatitis, or other dermatological condition that could be severe enough to impact this study Any other serious condition that could interfere with this study
Language abilities	<ul style="list-style-type: none"> Sufficient physical, cognitive, reading and linguistic capacities to allow patients to actively participate in the interview Patient speaks English fluently and can give documented informed consent 	
Other	<ul style="list-style-type: none"> <i>Photoguide interviews</i>: Is able to access the internet using a computer at the time of interview 	<ul style="list-style-type: none"> Patients who are known substance abusers

Abbreviations: AA, alopecia areata; JAKi, Janus kinase inhibitors; SALT, Severity of Alopecia Tool.

Online Resource 2 Clinical and demographic characteristics of patient interviews (Round 1 and 2) to develop ClinRO and PRO measures

Clinical/demographic characteristic	Round 1 (n=30)	Round 2 (n=15)	Total (n=45)
Clinical description, n (%)			
AA with ≥50% scalp hair loss and no eyebrow/eyelash loss	6 (20)	4 (27)	10 (22)
AA with ≥50% scalp hair loss with partial/full eyebrow and/or eyelash loss	24 (80)	11 (73)	35 (78)
Years since diagnosis, mean [SD; range]	11.7 [12.0; 1–47]	12.1 [10.1; 2–39]	11.8 [11.3; 1–47]
Most recent SALT score, mean [SD; range]	57.9 [40.4; 0–100]	85.9 [20.3; 50–100]	67.2 [37.2; 0–100]
JAKi experienced or naïve, n (%)			
JAKi-experienced patients	18 (60)	2 (13)	20 (44)
JAKi-naïve patients	12 (40)	11 (73)	23 (51)
Unknown*, either JAKi or placebo	-	2 (13)	2 (4)
Gender, n (%)			
Male	13 (43)	6 (40)	19 (42)
Female	17 (57)	9 (60)	26 (58)
Years of age, mean [SD; range]	35.2 [16.9; 15–72]	29.5 [8.4; 18–43]	33.3 [14.8; 15–72]
Ethnicity/race, n (%)			
Asian	5 (17)	4 (27)	9 (20)
Black or African American	1 (3)	1 (7)	2 (4)
White Caucasian	21 (70)	4 (27)	25 (56)
Hawaiian or Pacific Islander	0 (0)	1 (7)	1 (2)
Hispanic	0 (0)	5 (33)	5 (11)
Other	3 (10)	0 (0)	3 (7)
Education, highest certificate achieved, n (%)			
No high school diploma	6 (20)	3 (20)	9 (20)
High school diploma or equivalent	8 (27)	7 (47)	15 (33)
Associate's degree	2 (7)	0 (0)	2 (4)
Bachelor's degree or higher	14 (47)	5 (33)	19 (42)

Abbreviations: AA, alopecia areata; ClinRO, clinician-reported outcome; JAKi, Janus kinase inhibitor; PRO, patient-reported outcome; SALT, Severity of Alopecia Tool.

Note: due to rounding some percentages may not total 100%

* Two Round 2 patients were in a current clinical trial and it was unknown if they were receiving JAKi or placebo.

Online Resource 3 Quotes supporting measurement concepts

Concept	Quotes
Eyebrow/eyelash loss	<ul style="list-style-type: none"> – <i>“It is to do with the patient’s identity and the recognition of facial features and stuff. I think it’s a very, very crucial part of what defines a face, or recognition of someone’s face, and I think that holds true for both men and women.” –Clin-02</i> – <i>“It’s very, very, important for them not to have breaks, so even if the eyebrows thin, it looks continuous, it looks normal. But if it’s broken there’s a problem.” –Clin-08</i> – <i>“I think before I experienced scalp hair loss and like eyelash hair loss I was more self-conscious about it, because I mean some people do like stare.” –32-F</i> – <i>“I felt like I was wearing a mask. It was just the way that it looked was horrible to me. That’s it. I just was embarrassed, I preferred it when I wore my reading glasses to distract.” –24-F</i>
Eye irritation	<ul style="list-style-type: none"> – <i>“I like to work out a lot. And I played football for years. And sweat really just goes right into your eyes like – you can’t – it doesn’t – even like the no-eyelashes doesn’t help but like, no eyebrows, everything just goes right down into your eyes. It’s like tough to even see sometimes.” –37-M</i> – <i>“When I started losing my eyelashes and they’ve kind of come and gone, I noticed me eyes are much more irritated now. Like in the last couple of years, my eyes will get red, they burn, I feel like there’s stuff in my eyes.” –08-M</i>
Nail appearance/damage	<ul style="list-style-type: none"> – <i>“I think you would have to have pretty severe alopecia areata to have nail involvement, but it can be bothersome if it is really an advanced problem. The nails can be very rough, on the ends especially, they can tear easily. So, yes... that does bother patients, but if they have merely pitting, they don’t care about that.” –Clin-03</i> – <i>“Well, my nails have become very brittle. They break very easily. Normally that’s why I get them done, just because they’re always breaking.” –41-F</i>

Note: To anonymize the transcripts, codes were allocated which indicated the chronology of interviews, participant number, and, for patients, sex. For example, Clin-09 was the third dermatologists interviewed, and 33-F was the 33rd patient interviewed and female.

Online Resource 4 Development of ClinRO and PRO measures to assess eyebrow hair loss

First draft tested with dermatologists	Feedback & changes
<p>ClinRO measure</p> <p>Examine both eyebrows and select the best response below.</p> <p><input type="checkbox"/>₀ The eyebrows are bilaterally symmetric and have normal hair fullness (fill and density) when viewed at 2 feet away</p> <p><input type="checkbox"/>₁ The eyebrows are bilaterally symmetric and have moderate hair fullness (fill and density) when viewed at 2 feet away</p> <p><input type="checkbox"/>₂ The eyebrows are asymmetric or have minimal hair fullness (fill and density) when viewed at 2 feet away</p> <p><input type="checkbox"/>₃ No notable eyebrow hair</p>	<p>Item wording</p> <ul style="list-style-type: none"> • Dermatologists agreed that the distance for assessment should be standardized as two feet away; this instruction was added to the item wording. <p>Response options</p> <ul style="list-style-type: none"> • No dermatologist used the term ‘Fullness’ and some disliked the categorization of “Normal/ moderate/ minimal hair fullness.” Response options were therefore changed to ‘full coverage/minimal gaps/significant gaps.’ • The assessment of symmetry was refined as ‘even distribution.’
<p>PRO measure</p> <p>Look at the hair in both of your eyebrows. Please rate your eyebrows, as they look today.</p> <p>Please select one answer.</p> <p><input type="checkbox"/>₀ I have full eyebrow hair and my eyebrows look the same (symmetrical)</p> <p><input type="checkbox"/>₁ I have some eyebrow hair and my eyebrows look the same (symmetrical)</p> <p><input type="checkbox"/>₂ I do not have much eyebrow hair or my eyebrows do not look the same (not symmetrical)</p> <p><input type="checkbox"/>₃ I have no eyebrows</p>	<p>Item wording</p> <ul style="list-style-type: none"> • Patients’ ability and preference for rating each eyebrow separately or together was investigated in Round 2. <ul style="list-style-type: none"> ○ All 15 patients could rate their eyebrows together; 5/12 patients stated a preference for rating the left and right eyebrows together, 7/12 expressed preference to rate their eyebrows separately. With near equivalent preferences, simultaneous rating was retained. <p>Response options</p> <ul style="list-style-type: none"> • Based on dermatologist feedback (see row above), fullness and symmetry were revised to assess gaps and thinning; an additional instruction was added for patients to respond thinking about the aspect that bothered them most.

Abbreviations: ClinRO, clinician-reported outcome; PRO, patient-reported outcome.

Online Resource 5 Development of ClinRO and PRO measures to assess eyelash hair loss

First draft tested with dermatologists	Feedback & changes
<p>ClinRO measure</p> <p>Examine both eyelashes and select the best response below.</p> <p><input type="checkbox"/>₀ The eyelashes are present on each eye and have normal hair fullness and length</p> <p><input type="checkbox"/>₁ The eyelashes are present on each eye and have moderate hair fullness and length</p> <p><input type="checkbox"/>₂ The eyelashes are on only one eye or have minimal hair fullness and length</p> <p><input type="checkbox"/>₃ No notable eyelashes on either eye</p>	<p>Item wording</p> <ul style="list-style-type: none"> Some dermatologists felt it was unclear whether the investigator should consider the upper, lower, or both eyelids; an instruction to assess upper and lower eyelashes was added. <p>Response options</p> <ul style="list-style-type: none"> No dermatologist used the term ‘Fullness,’ and some disliked the terms ‘normal/moderate/minimal fullness.’ Response options were therefore changed to assess continuity/even spacing, and ‘minimal’ or ‘significant’ gaps in coverage. Dermatologists did not consider length to be an important assessment; this concept was therefore removed.
<p>PRO measure</p> <p>Look at the hair in all of your eyelashes. Please rate your eyelashes, as they look today. Please select one answer.</p> <p><input type="checkbox"/>₀ I have full eyelashes on both eyes</p> <p><input type="checkbox"/>₁ I have some eyelashes on both eyes</p> <p><input type="checkbox"/>₂ I do not have many eyelashes or I only have eyelashes on one eye</p> <p><input type="checkbox"/>₃ I have no eyelashes</p>	<p>Item wording</p> <ul style="list-style-type: none"> In Round 1, patients felt assessment of upper and lower eyelashes was relevant (although some considered top eyelashes to be more important), 11 patients preferred the eyelash ClinRO and suggested that the PRO measure should reference the upper and lower eyelashes (n=5) and the spacing of the eyelashes (n=4). Therefore, an instruction was added to this effect. Patients’ ability and preference for rating each eyelash separately or together was investigated in Round 2. <ul style="list-style-type: none"> All 14 patients queried could rate their eyelashes together. 6/14 patients preferred to assess left and right eyes separately and 8/14 patients preferred to rate both eyes together. With near equivalent preferences, simultaneous rating was retained. <p>Response options</p> <ul style="list-style-type: none"> Based on dermatologist feedback (see row above), fullness was revised to gaps

Abbreviations: ClinRO, clinician-reported outcome; PRO, patient-reported outcome.

Online Resource 6 Development of a PRO measure to assess eye irritation

First draft tested with dermatologists	Feedback & changes
<p>Have either of your eyes been dry in the past 24 hours? Please select one answer.</p> <p><input type="checkbox"/>₀ Not at all dry</p> <p><input type="checkbox"/>₁ A little dry</p> <p><input type="checkbox"/>₂ Moderately dry</p> <p><input type="checkbox"/>₃ Very dry</p>	<p>Item wording & response options</p> <ul style="list-style-type: none"> • Dermatologists informed change of measurement concept from eye dryness to eye irritation as dryness was considered irrelevant. • In Round 1 patient interviews, the item was interpreted inconsistently e.g. in terms of severity or irritation (n=12); frequency or intermittency of irritation (n=5); or both frequency and severity of eye irritation (n=2). <ul style="list-style-type: none"> ○ Therefore, example definitions of the term ‘irritated’ were included in the instructions and the response options were revised to indicate severity rather than frequency. ○ In Round 2 a similar pattern was observed, however, both severity and frequency were integral to how patients determined severity. <p>Recall period</p> <ul style="list-style-type: none"> • Dermatologists informed a change in recall period from ‘past 24 hours’ to ‘past 7 days.’

Abbreviations: PRO, patient-reported outcome.

Online Resource 7 Development of ClinRO and PRO measures to assess nail appearance

Original version tested with dermatologists	Feedback & changes
<p>ClinRO measure</p> <p>Dermatologist descriptions of nail involvement were collected in interviews; an item was crafted in the SPM (but not debriefed in full with dermatologists).</p>	<p>Item wording</p> <ul style="list-style-type: none"> • During the SPM, dermatologists considered it important to ask patients if toenail damage was important to them and whether they would be comfortable with a clinician assessing their toenails. • Patient interviews confirmed that most patients thought that toenails should be assessed in addition to fingernails, and would be comfortable with toenail assessment by the clinician.
<p>PRO measure</p> <p>Look at your nails. Please rate your nails, as they look today. Please select one answer.</p> <p><input type="checkbox"/>₀ Not at all damage (rough, split, discolored, or brittle)</p> <p><input type="checkbox"/>₁ A little damage (rough, split, discolored, or brittle)</p> <p><input type="checkbox"/>₂ Moderately damage (rough, split, discolored, or brittle)</p> <p><input type="checkbox"/>₃ Very damage (rough, split, discolored, or brittle)</p>	<p>Response options</p> <ul style="list-style-type: none"> • Dermatologists informed removal of the damage descriptor ‘discolored’ as this was an infrequent problem. • Dermatologists informed the addition of the damage descriptor ‘pitting’ as this was a common problem.

Abbreviations: ClinRO, clinician-reported outcome; PRO, patient-reported outcome; SPM, small panel meeting.

Online Resource 8 Clinical and demographic characteristics of patient interviews to develop eyebrow, eyelash and nail photoguides

Clinical/demographic characteristic	Patients n (%) [N=10]
Eyebrow hair loss (partial or complete), n (%)¶	
Current eyebrow hair loss	9 (90)
Previous eyebrow hair loss	1 (10)
Eyelash hair loss (partial or complete), n (%)¶	
Current eyelash hair loss	8 (80)
Previous eyelash hair loss	2 (20)
Nail damage, n (%)¶	
Current nail damage	3 (30)
Previous nail damage	3 (30)
No experience of nail damage	4 (40)
Years since diagnosis, mean [SD; range]§	15.2 [12.0; 2–42]
Scalp hair loss, n (%)§	
Current scalp hair loss ≥50%	6 (60)
Previous experience of scalp hair loss ≥50%	4 (40)
Current treatment, n (%)‡	
JAKi	2 (20)
Unknown, either JAKi or placebo (participating in blinded clinical trial)	1 (10)
Experience of JAKi treatment, n (%)	
Currently receiving JAKi treatment	2 (20)
Previous experience with JAKi treatment	3 (30)
Experience unknown, currently/previous in blinded clinical trial	2 (20)
No experience with JAKi	3 (30)
Gender, n (%)	
Male	3 (30)
Female	7 (70)
Years of age, mean [SD; range]	37.0 [9.2; 21–54]
Race/ethnicity, n (%)	
White Caucasian	9 (90)
Hawaiian or Pacific Islander	1 (10)
Education (highest level completed), n (%)	
High school, no diploma	1 (10)
High school diploma	1 (10)
Some college, no degree	2 (20)
Bachelor's degree	4 (40)
Master's degree	2 (20)

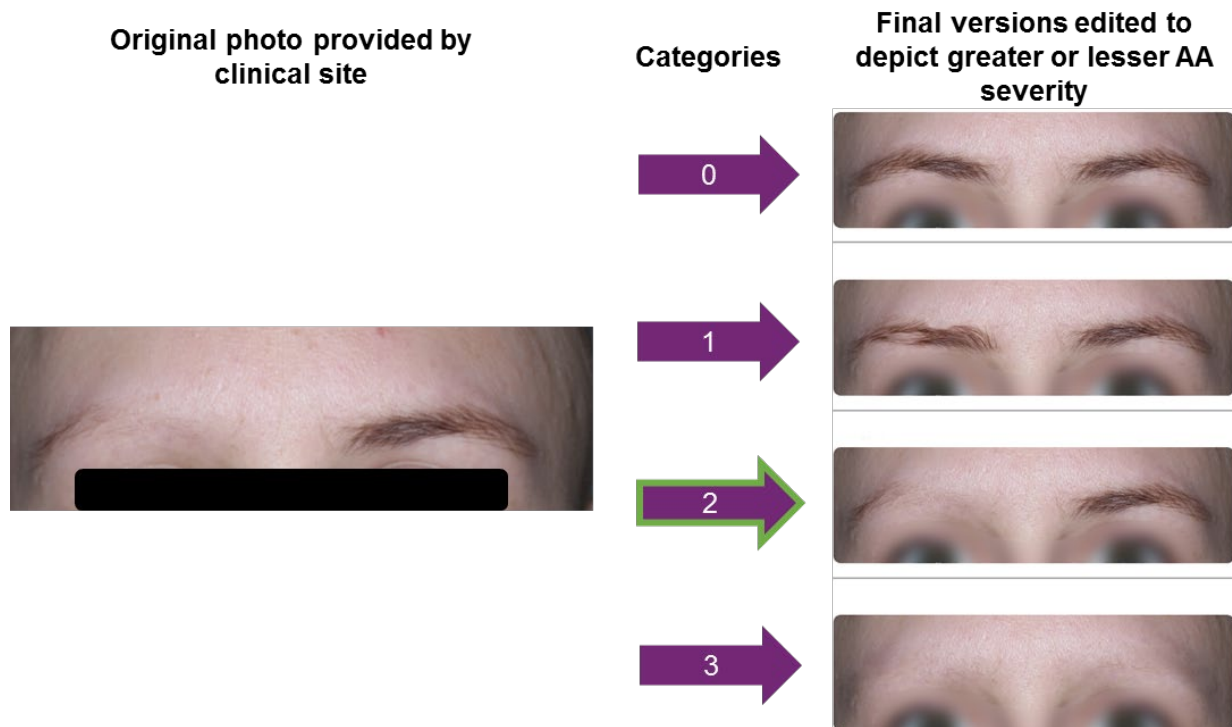
¶These data were reported by the patient during the patient interview

§These data were reported by the clinical site using the Case Report Form. Dermatologists took this data from medical records and/or from discussion with the patient.

‡Non-mutually exclusive

Abbreviations: JAKi, Janus Kinase inhibitor.

Online Resource 9 Example comparison of the original photo depicting a patient with eyebrow hair loss compared to the edited versions used in the final ClinRO Measure for Eyebrow Hair Loss™ and PRO Measure for Eyebrows™ photoguides



ClinRO categories:

- 0-The eyebrows have full coverage and no areas of hair loss
- 1-There are minimal gaps in eyebrow hair and distribution is even
- 2-There are significant gaps in eyebrow hair or distribution is not even
- 3-No notable eyebrow hair

Patient in original photo was rated as category 2 by their dermatologist.

Abbreviations: AA, alopecia areata; ClinRO, clinician-reported outcome; PRO, patient-reported outcome.

Online Resource 10 Photoguides for the ClinRO Measure for Eyebrow Hair Loss™, ClinRO Measure of Eyelash Hair Loss™, ClinRO Measure for Nail Appearance™, PRO Measure for Eyebrows™, PRO Measure for Eyelashes™ and PRO Measure for Nail Appearance™

Please note:

The photoguides for the ClinRO Measure for Eyebrow Hair Loss™, ClinRO Measure of Eyelash Hair Loss™, ClinRO Measure for Nail Appearance™, PRO Measure for Eyebrows™, PRO Measure for Eyelashes™ and PRO Measure for Nail Appearance™ on the following pages are subject to copyright owned by Eli Lilly and Company. Permission to use is granted under Creative Commons attribution-No derivatives 4.0 International License. Contact Eli Lilly and Company in the event of any proposed modification.

The photoguides are formatted to US Legal (8.5" x 14") paper size.

ClinRO Measure for Eyebrow Hair Loss™

Examine **both eyebrows** from **two feet away** and select the best response.

The eyebrows have full coverage and no areas of hair loss



There are minimal gaps in eyebrow hair **and** distribution is even



There are significant gaps in the eyebrow hair **or** distribution is not even



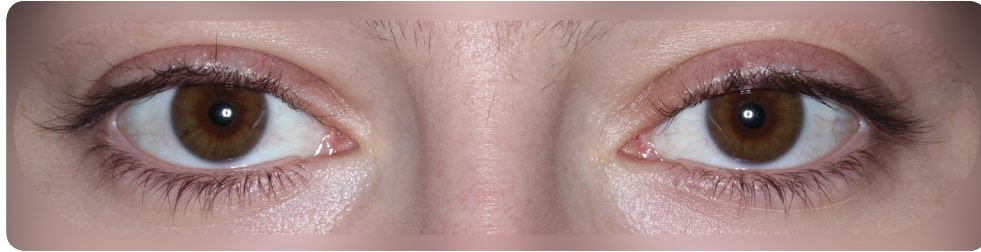
No notable eyebrow hair



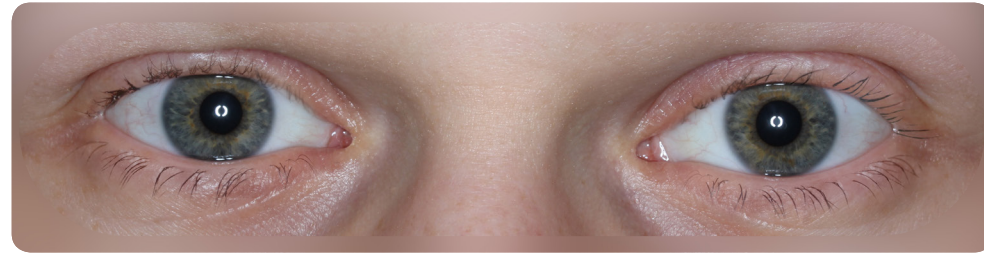
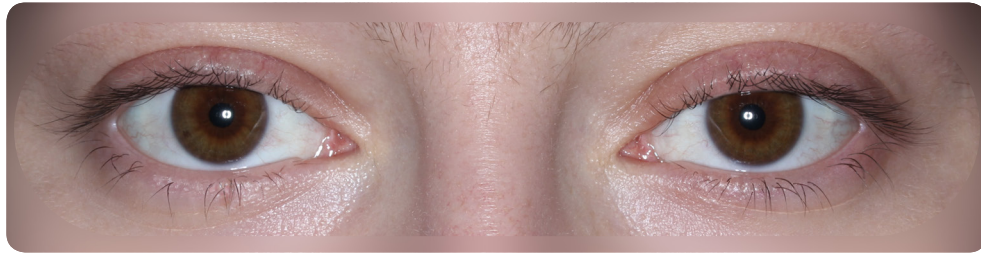
ClinRO Measure for Eyelash Hair Loss™

Examine the **upper and lower eyelashes** of **both eyes** and select the best response.

The eyelashes form a continuous line along the eyelids on both eyes



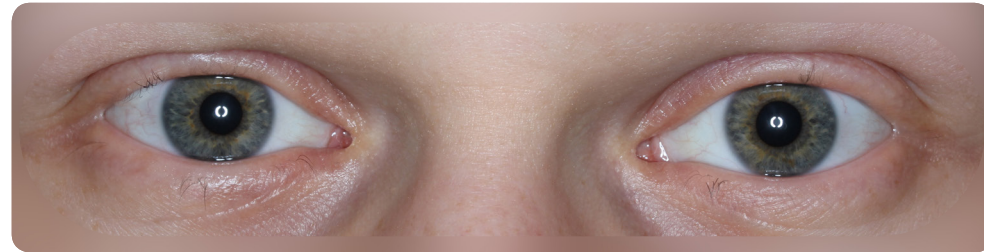
There are minimal gaps **and** the eyelashes are evenly spaced along the eyelids on both eyes



There are significant gaps along the eyelids **or** the eyelashes are not evenly spaced along the eyelids



No notable eyelashes



ClinRO Measure for Nail Appearance™

Examine the **fingernails and toenails** and select the best response.

Nails are not at all damaged (e.g. pitted, rough, brittle, split)



At least one nail is a little damaged (e.g. pitted, rough, brittle, split)



At least one nail is moderately damaged (e.g. pitted, rough, brittle, split)



At least one nail is very damaged (e.g. pitted, rough, brittle, split) **or** patient has lost at least one nail



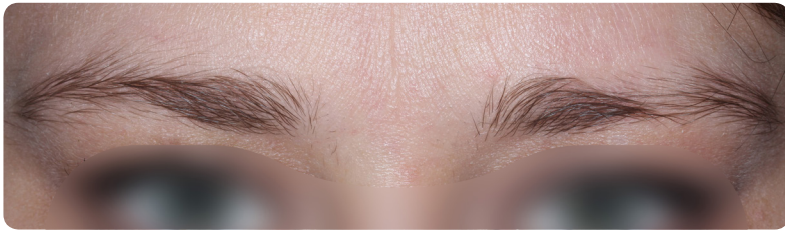
PRO Measure for Eyebrows™

Look at the **hair in both of your eyebrows**. Please rate your eyebrows, as they look **today**. This question asks about **gaps(s)** in your eyebrows or **thinning** in your eyebrows. If you have gap(s) in your eyebrows and thinning in your eyebrows, please choose your answer based on the type of hair loss that bothers you the most. Please select **one** answer.

I have full eyebrows on each eye



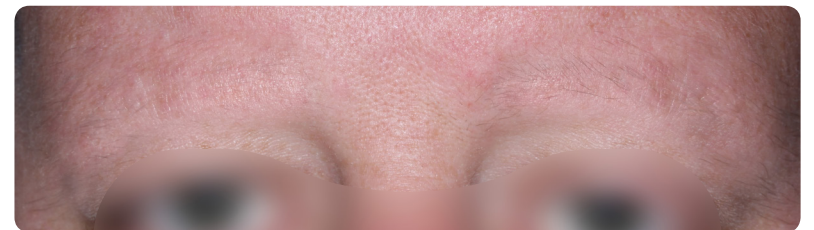
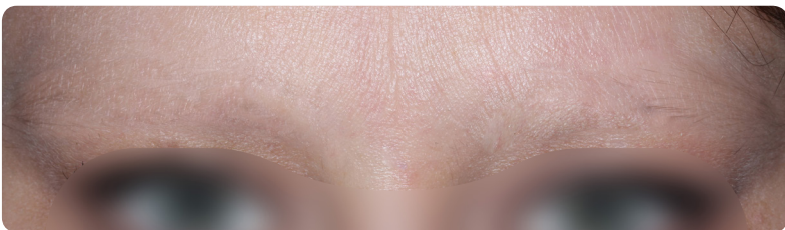
I have a minimal gap(s) **or** a minimal amount of thinning in at least one of my eyebrows



I have a large gap(s) **or** a large amount of thinning in at least one of my eyebrows



I have no or barely any eyebrow hairs

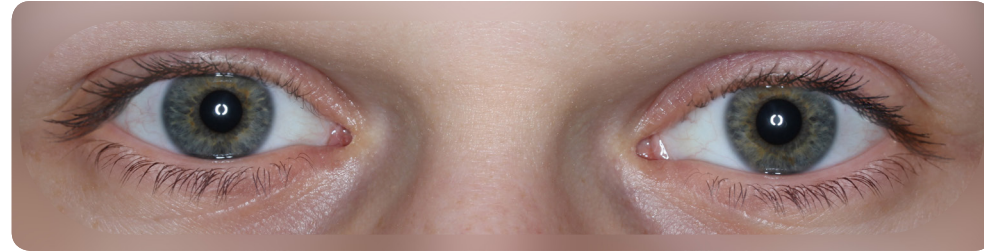
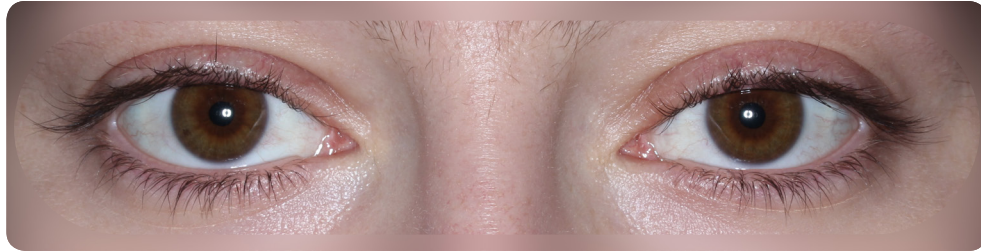


PRO Measure for Eyelashes™

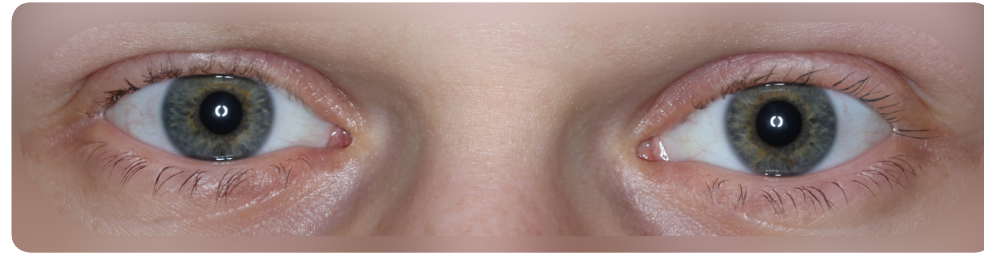
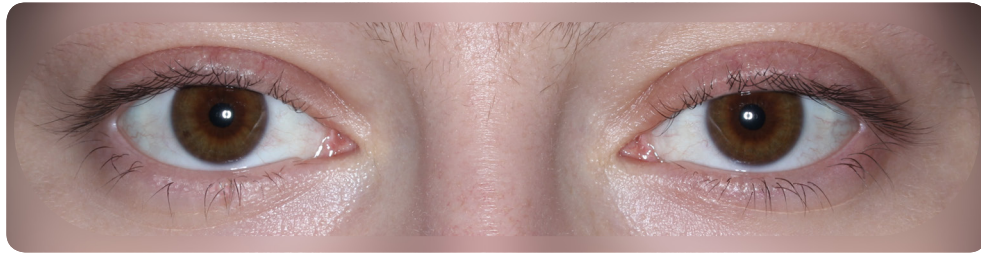
Look at **your upper and lower eyelashes on both your eyes**. Please rate your eyelashes, as they look **today**.

Please select **one** answer.

I have full eyelashes on each eyelid



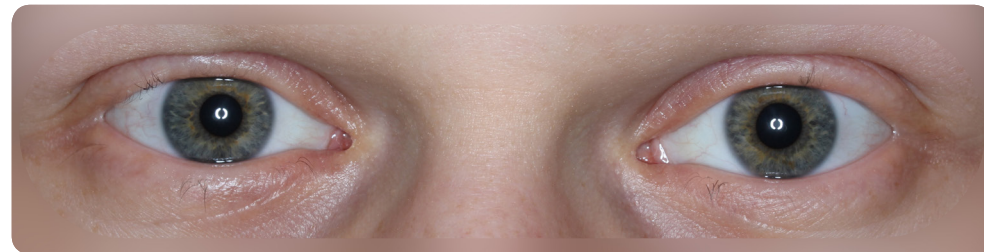
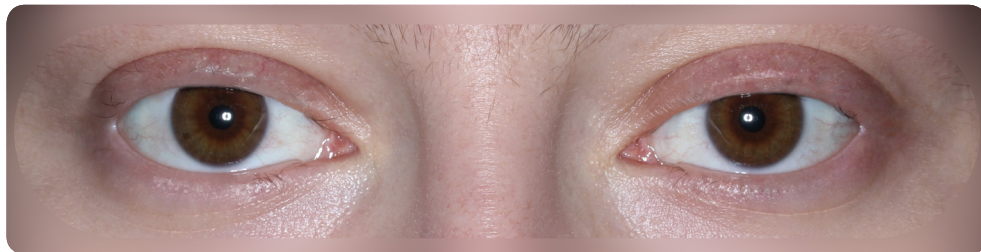
I have a minimal gap **or** minimal gaps along the eyelids



I have a large gap **or** large gaps along the eyelids



I have no **or** barely any eyelash hair



PRO Measure for Nail Appearance™

Examine your **fingernails and toenails**. Please rate your fingernails and toenails, as they look **today**.

Please select **one** answer.

Nails are not at all damaged (e.g. pitted, rough, brittle, split)



At least one nail is a little damaged (e.g. pitted, rough, brittle, split)



At least one nail is moderately damaged (e.g. pitted, rough, brittle, split)



At least one nail is very damaged (e.g. pitted, rough, brittle, split) **or** you have lost at least one nail

