National Eye Institute

Coalition for
Usher Syndrome Research
May 13, 2013

Protocol 05-EI-0096
Usher Syndrome Natural History and Molecular Genetics

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National Eye Institute

05-EI-0096 Summary

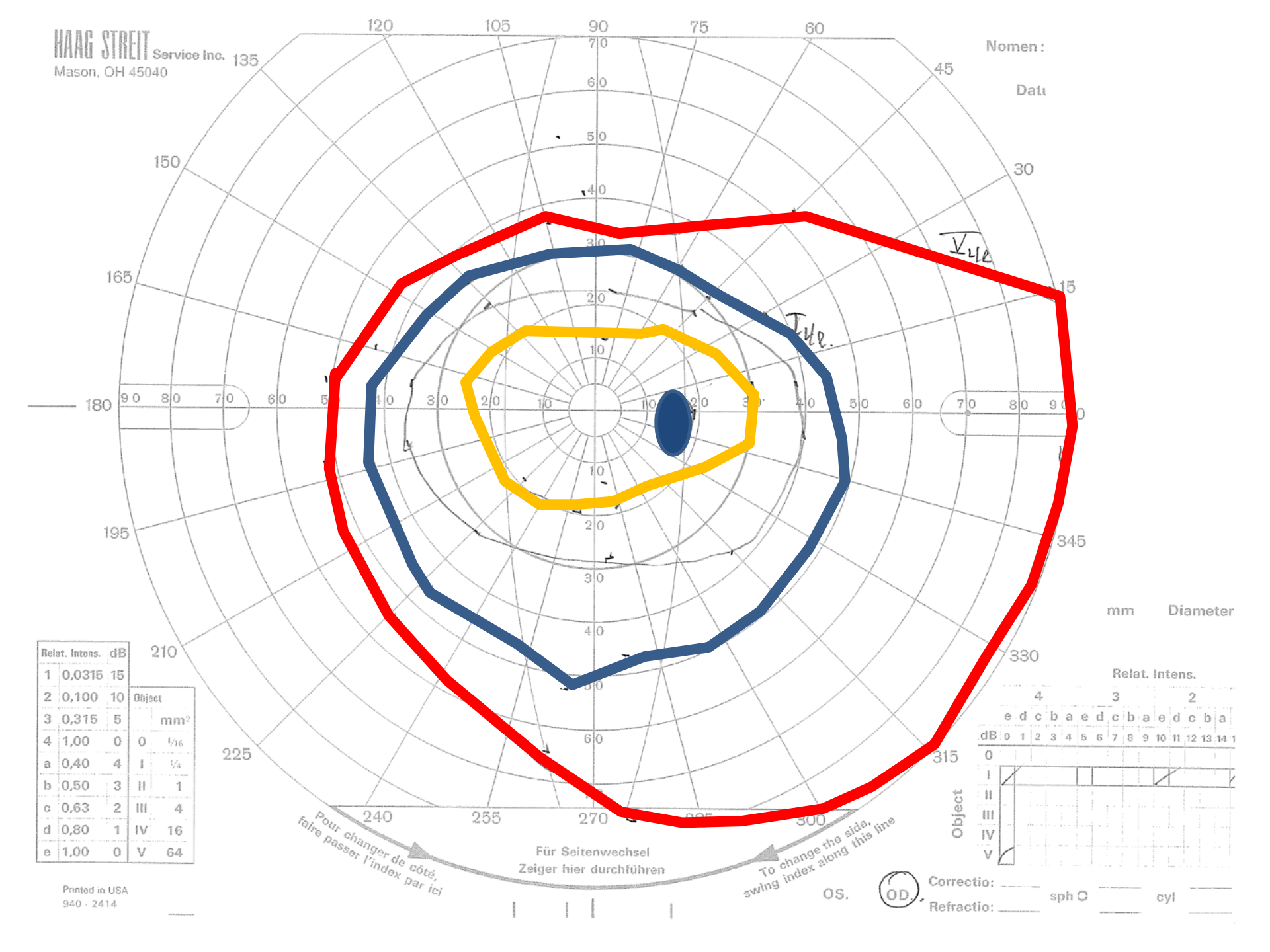
- Enroll patients with Usher syndrome phenotype
- Detailed phenotyping to characterize clinical findings:
  - Ophthalmic exam / Visual function assessment
  - Audiology
  - Vestibular function
- Molecular analysis and genetic counseling
- Return visit in 2-5 years to assess natural history of disease

Visual Function Assessment

- Visual acuity:
  - Measure of central visual function
  - Tends to be near normal in earlier stages of the disease in most Usher syndrome patients
  - Best-corrected acuity is usually recorded and indicated correction of refractive error (myopia, hyperopia, astigmatism)
  - Affected by ocular changes associated with Usher syndrome such as: cataract, macular edema, epiretinal membranes…

Visual Function Assessment

- Visual Field:
  - Measure of peripheral (side) vision
  - Usually affected early in disease process: midperipheral defects (scotomas) of varying size and depth are noted early in the disease process
  - Significant constriction in advanced stages of the disease lead to “tunnel vision”; sometimes a preserved peripheral island is maintained
  - Multiple approaches / techniques are available for visual field measurement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Mason, OH 45040
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135 45
150 30
165 15
180 0
195 345
210 330
225 315
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90 80 70 60 50 40 30 20 10
V4e
I4e.
Relat. Intens. dB
1 0,0315 15
2 0,100 10
3 0,315 5
4 1,00 0
a 0,40 4
b 0,50 3
c 0,63 2
d 0,80 1
e 1,00 0
Object
mm²
0 1/16
I 1/4
II 1
III 4
IV 16
V 64
Printed in USA
940 - 2414
Pour changer de côté, faire passer l'index par ici
Für Seitenwechsel Zeiger hier durchführen
To change the side, swing index along this line
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Relat. Intens.
4 3 2
e d c b a e d c b a e d c b a
dB 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 1
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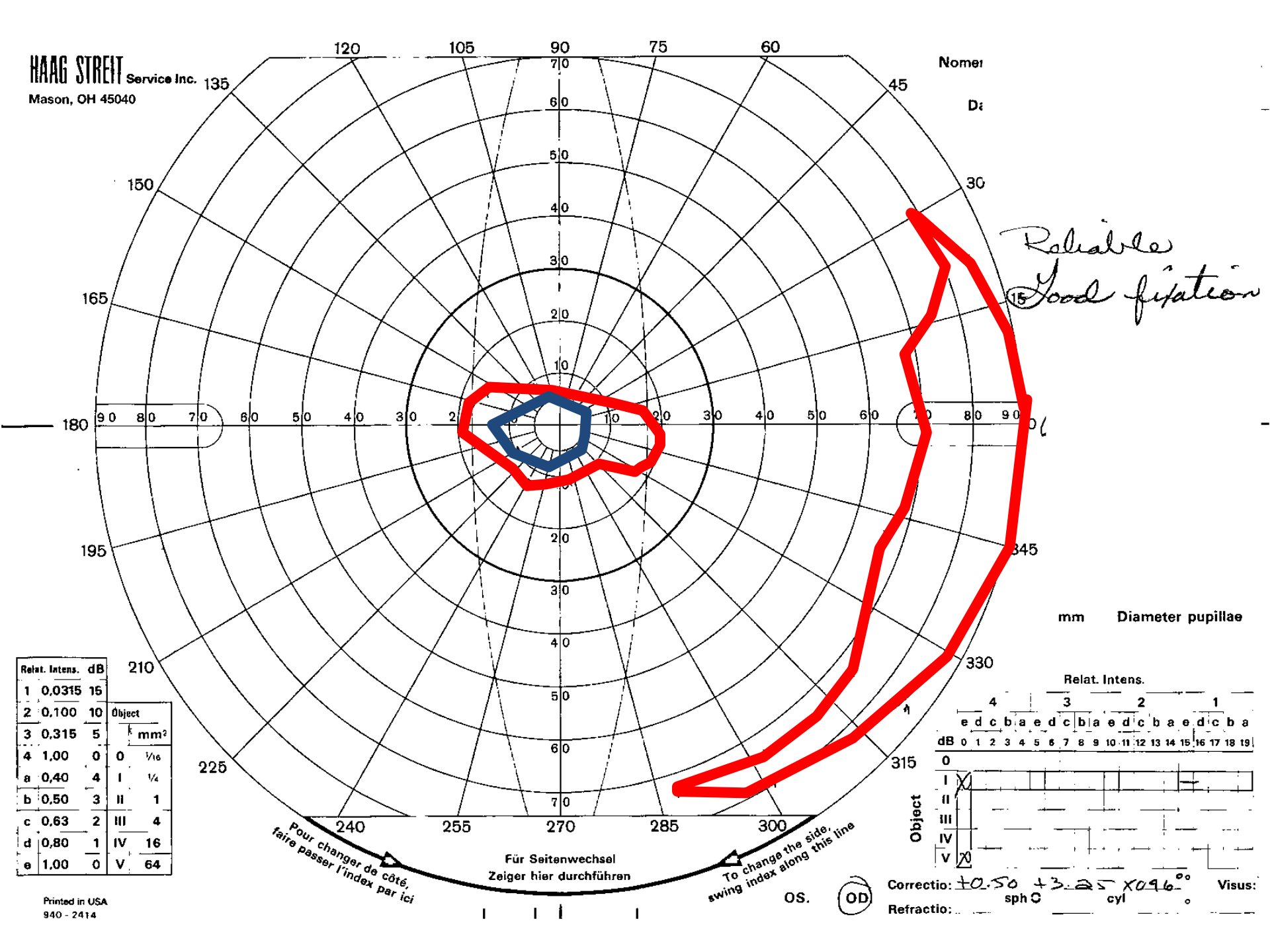
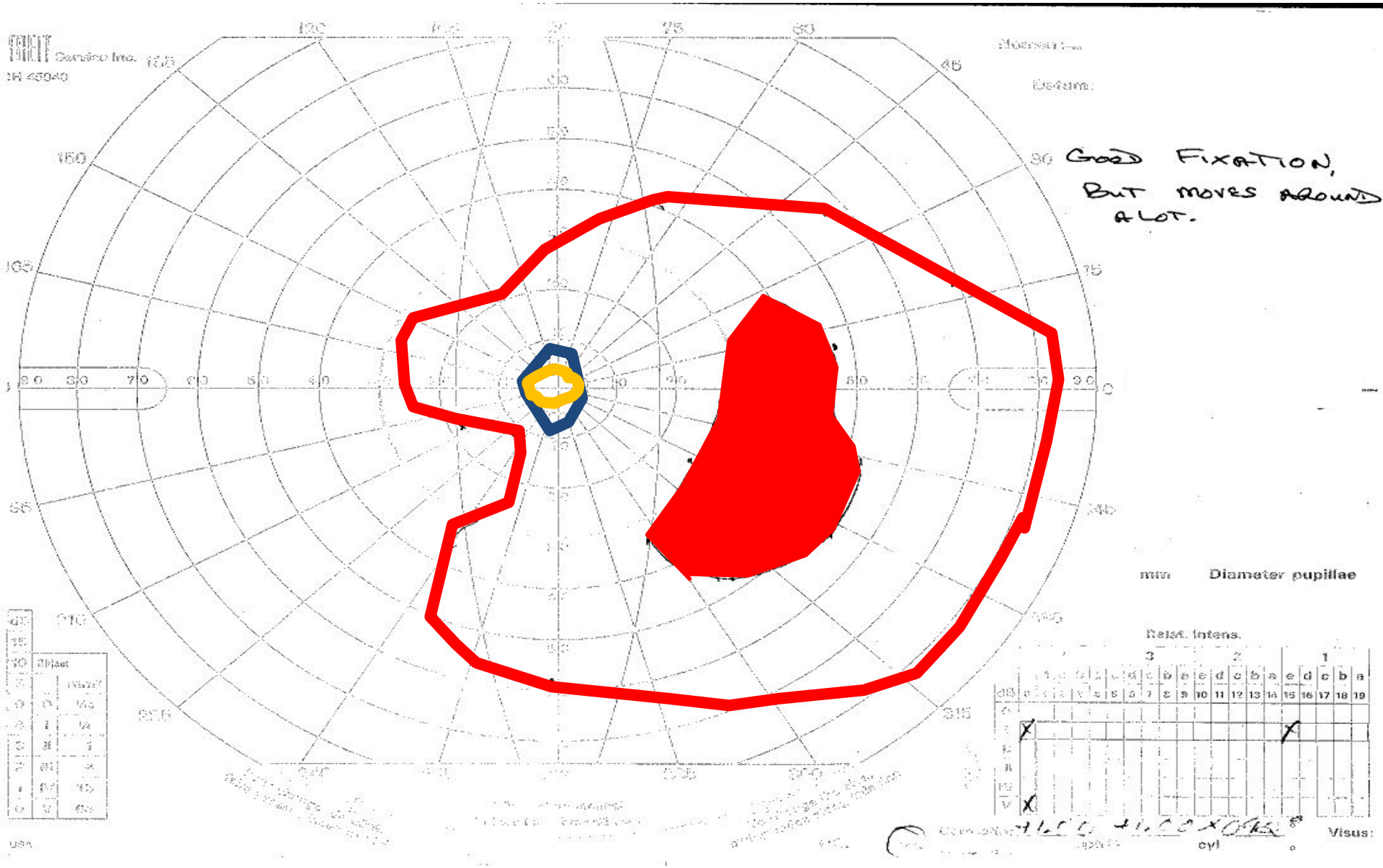
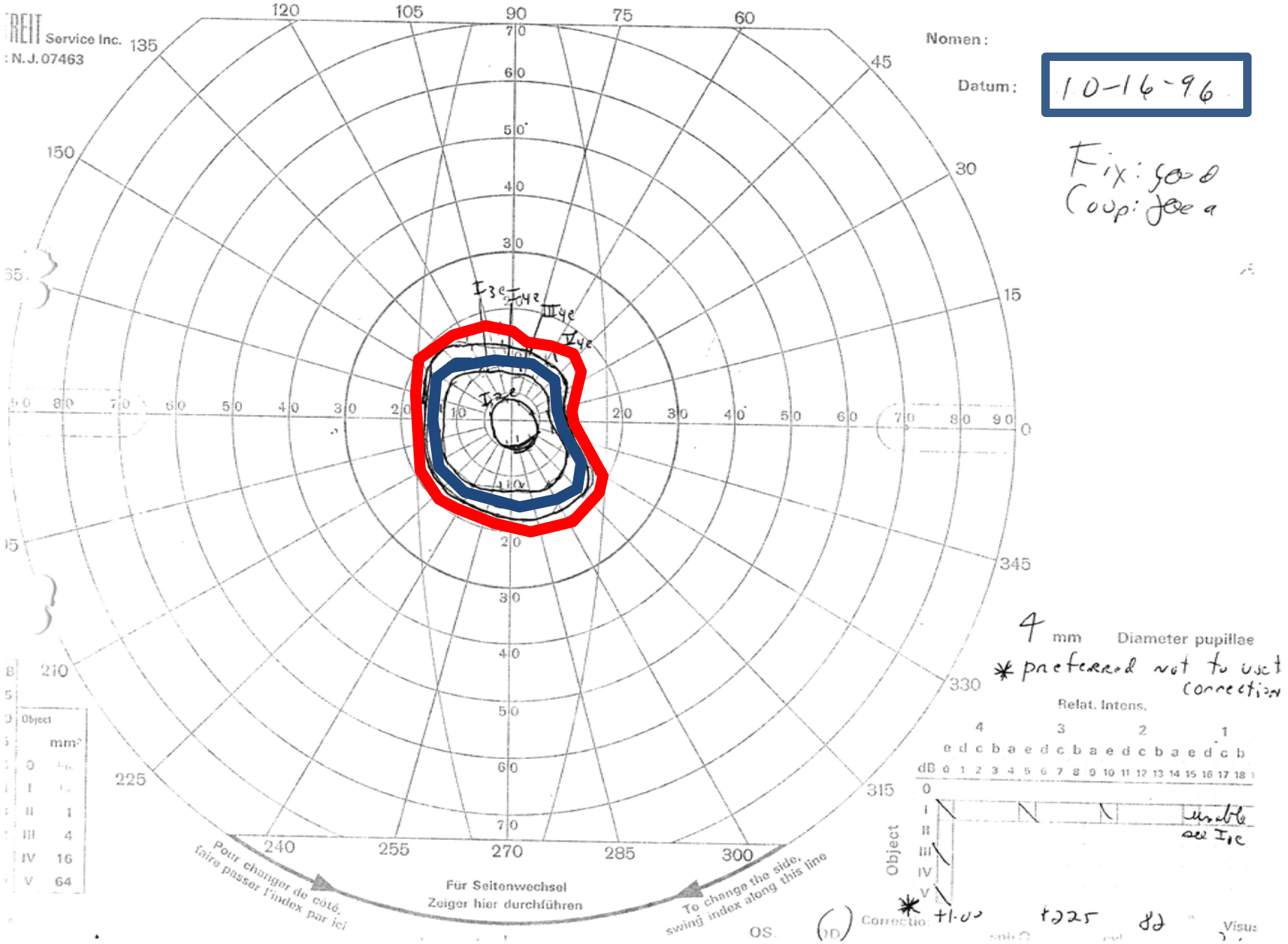


Relat. Intens.		dB
1	0,0315	15
2	0,100	10
3	0,315	5
4	1,00	0
a	0,40	4
b	0,50	3
c	0,63	2
d	0,80	1
e	1,00	0

Object	
	mm²
0	1/16
I	1/4
II	1
III	4
IV	16
V	64


GOOD FIXATION,
BUT MOVES AROUND
A LOT.
mm Diameter pupillae
Visus:


REIT Service Inc.
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Nomen:
Datum: 10-16-96
Fix: good
Coop: fair
I3e I4e III4e II4e I2e
4 mm Diameter pupillae
* preferred not to use correction
Relat. Intens.
4 3 2 1
e d c b a e d c b a e d c b a e d c b
dB 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Object
I
II
III
IV
V
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Object
mm²
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I ¼
II 1
III 4
IV 16
V 64
Pour changer de côté, faire passer l'index par ici
Für Seitenwechsel Zeiger hier durchführen
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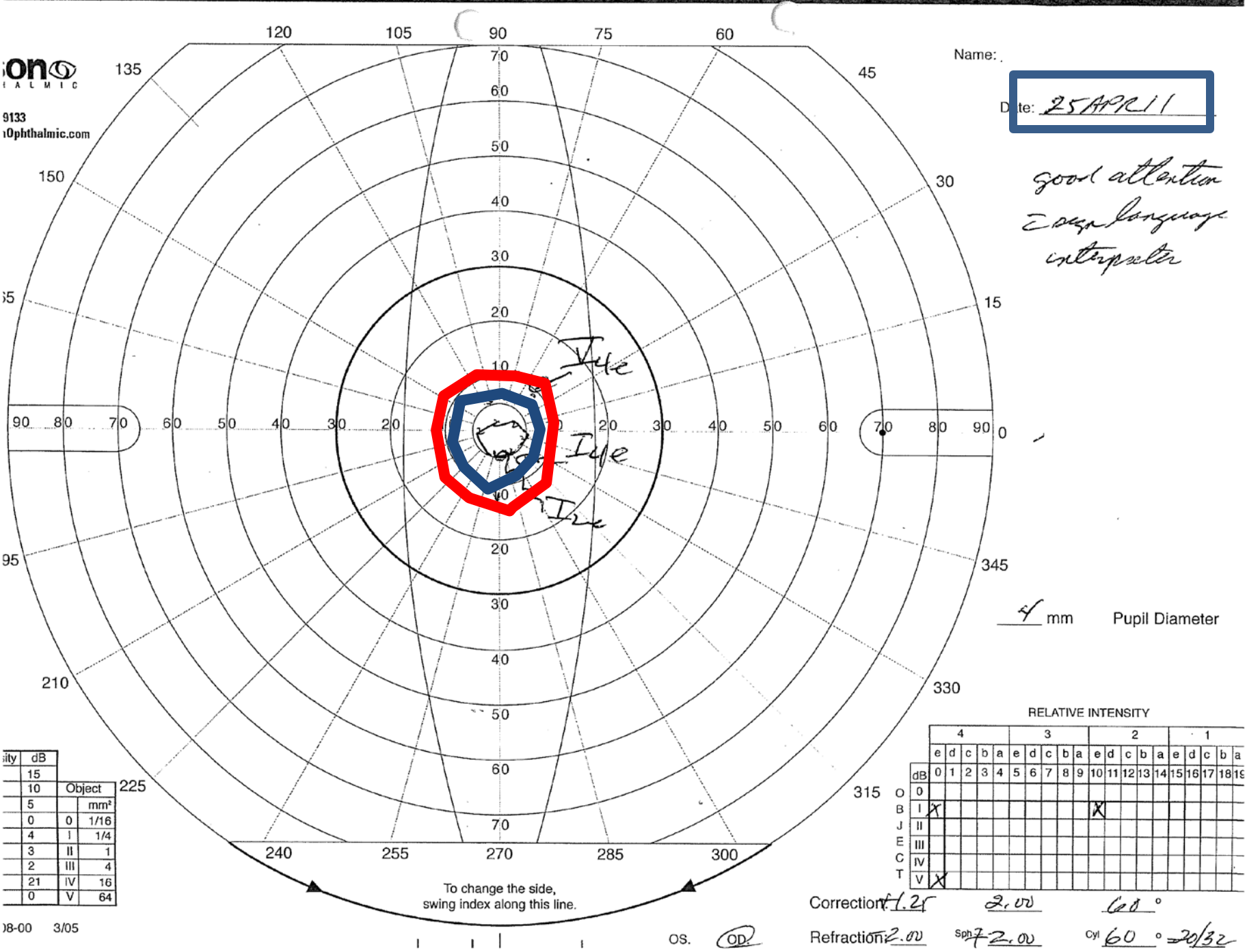
82
Visu

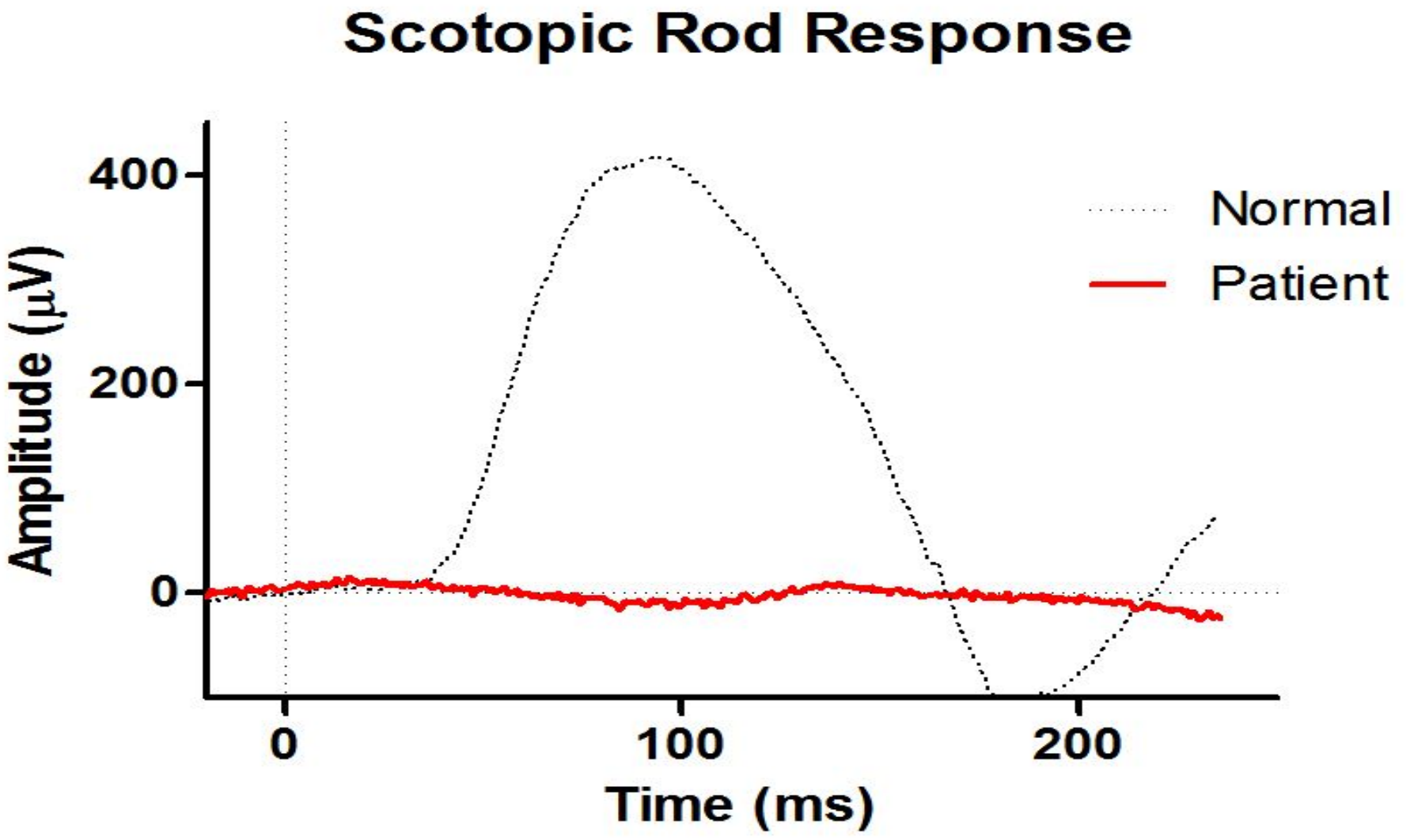

Name:
Date: 25 APRIL
good attention
Eng language
interpreter
Blue
Blue
Blue
4 mm Pupil Diameter
RELATIVE INTENSITY
To change the side,
swing index along this line.
OS. OD.
Correction +1.25 2.00 60 °
Refraction +2.00 Sph +2.00 Cyl 60 ° 20/32
9133
Ophthalmic.com
08-00 3/05

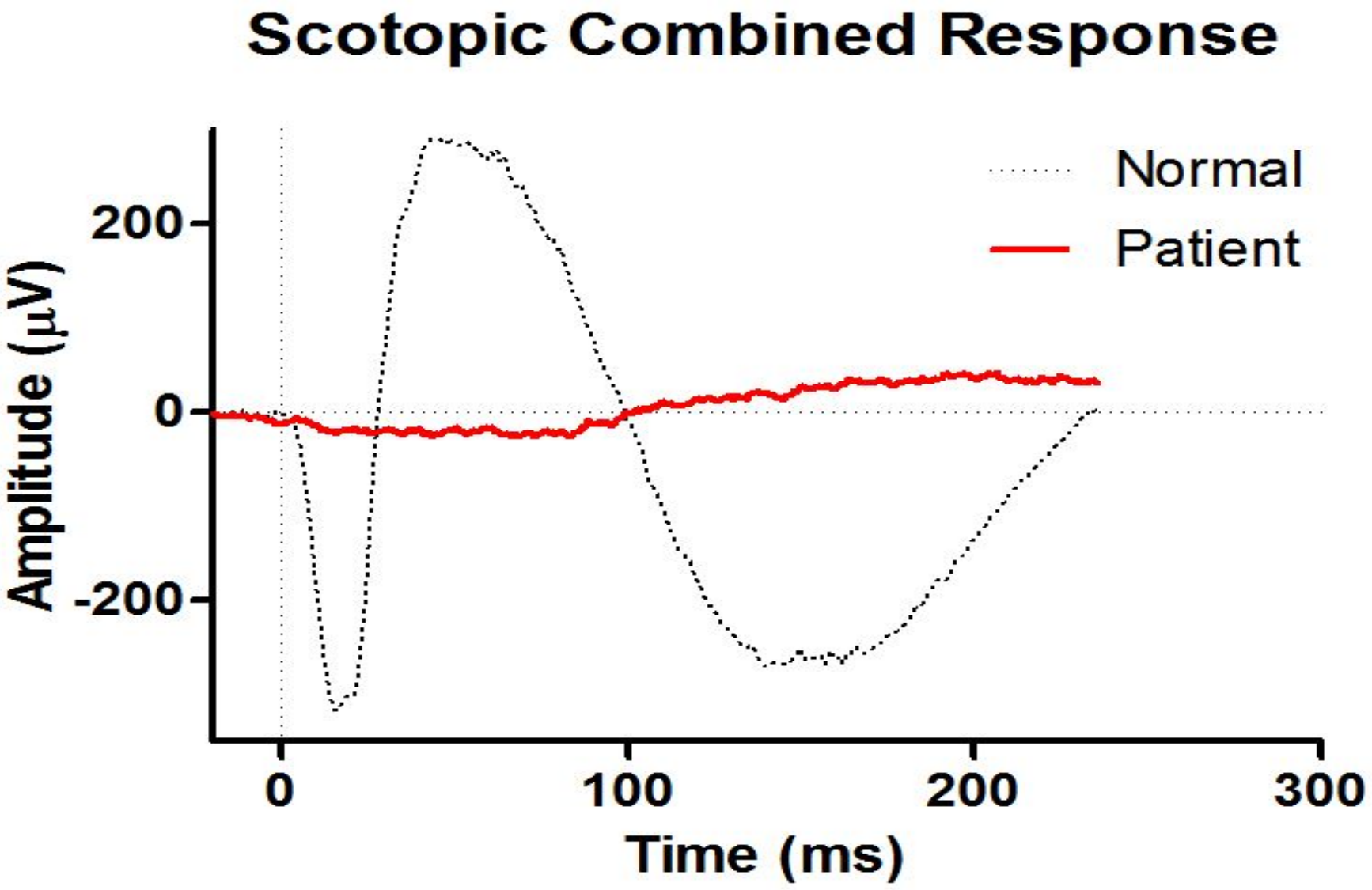
Visual Function Assessment

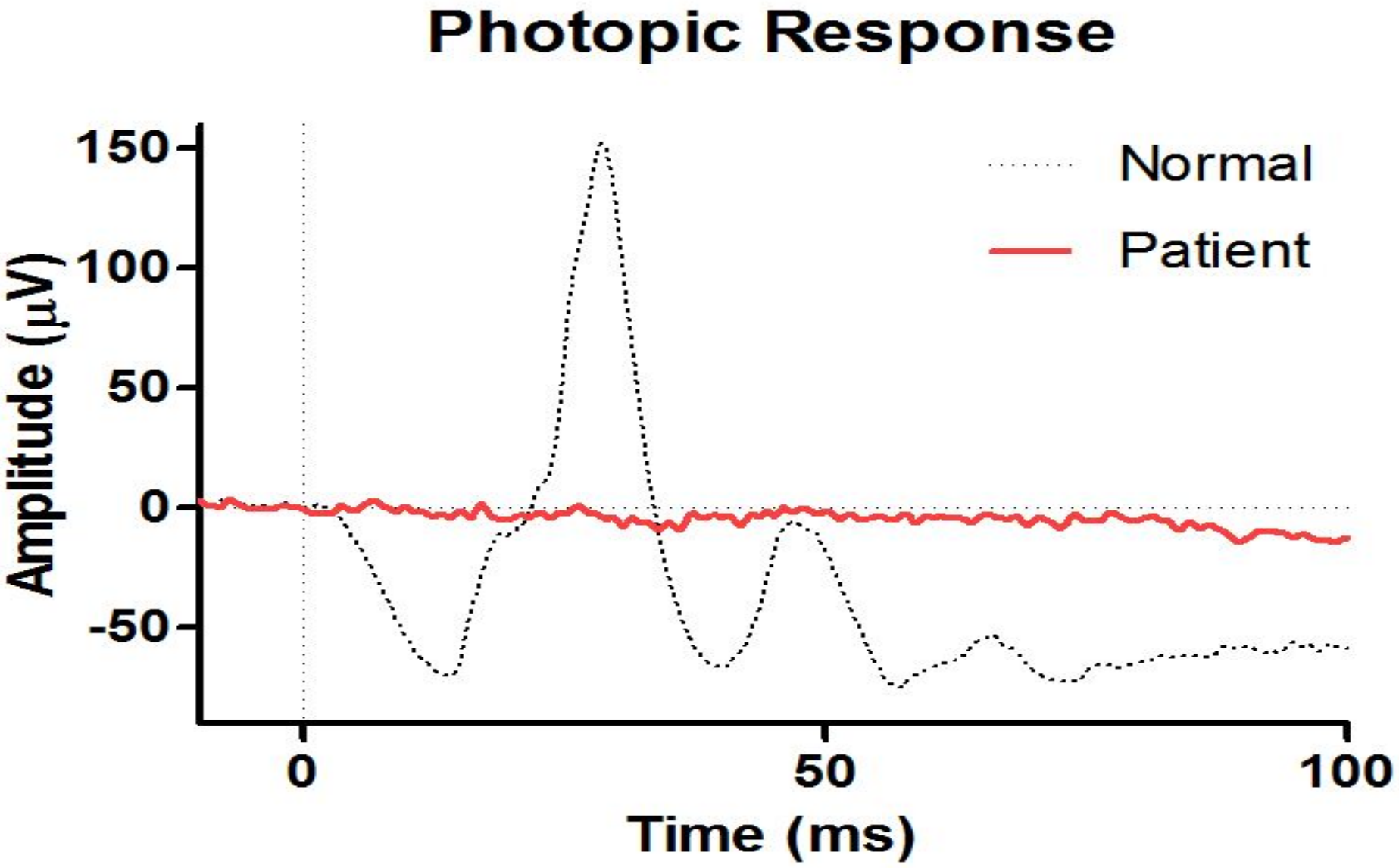
- Dark adaptometry:
  - Measures the speed of adaptation to a change in light exposure and the final level of adaptation
  - Central and peripheral measurements can be obtained
  - Tends to be significantly affected early in the disease process
- Color vision and Contrast sensitivity:
  - Measures of central cone function

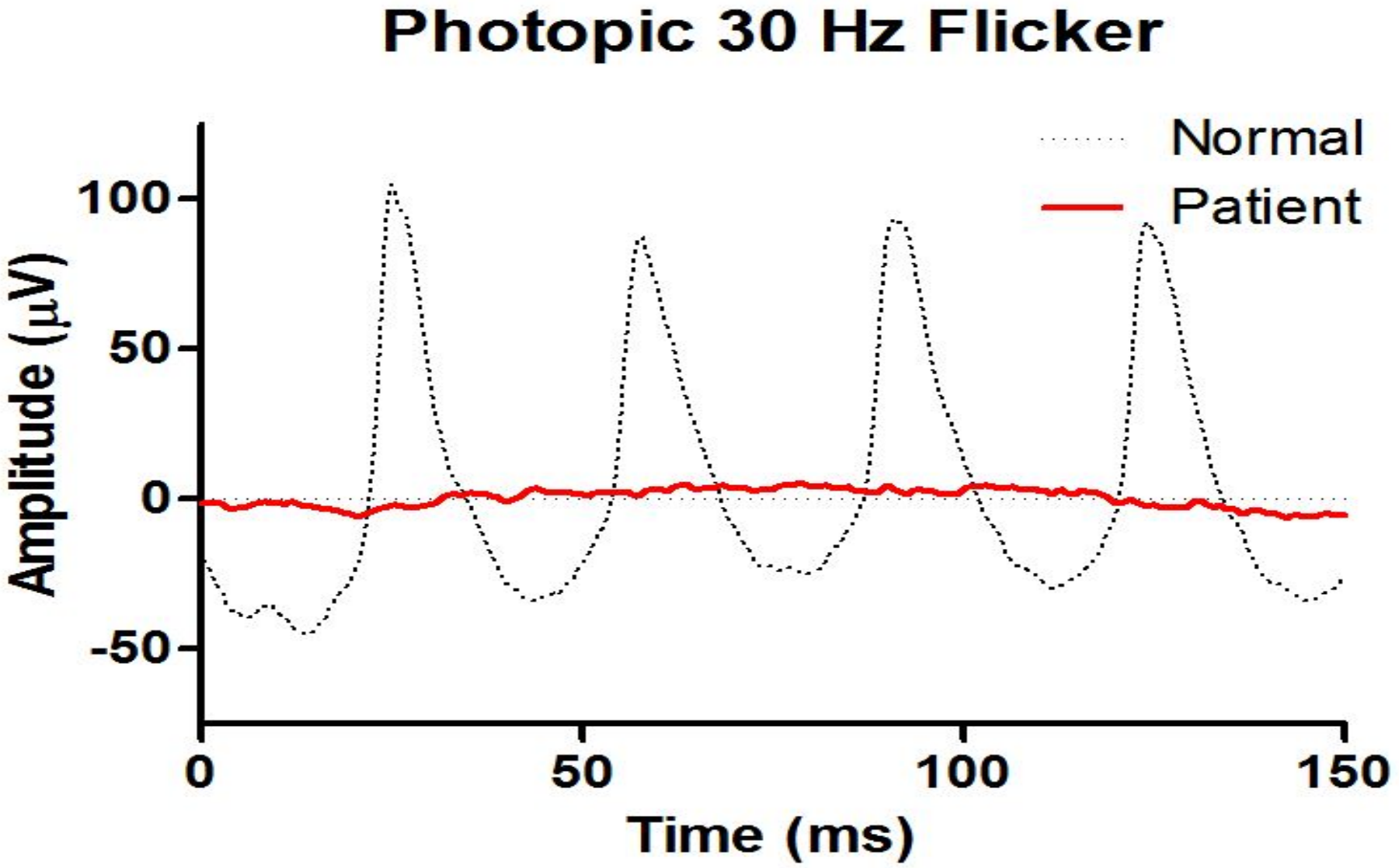
Electroretinography

- Electrical response of the retina to light stimulation
  - Scotopic / Dark-adapted responses: measured following a period of dark adaptation; often used to measure rod-driven responses; cone system kicks in at brighter intensities
  - Photopic / Light-adapted responses: measured after a period of light adaptation; used to measure cone-driven responses

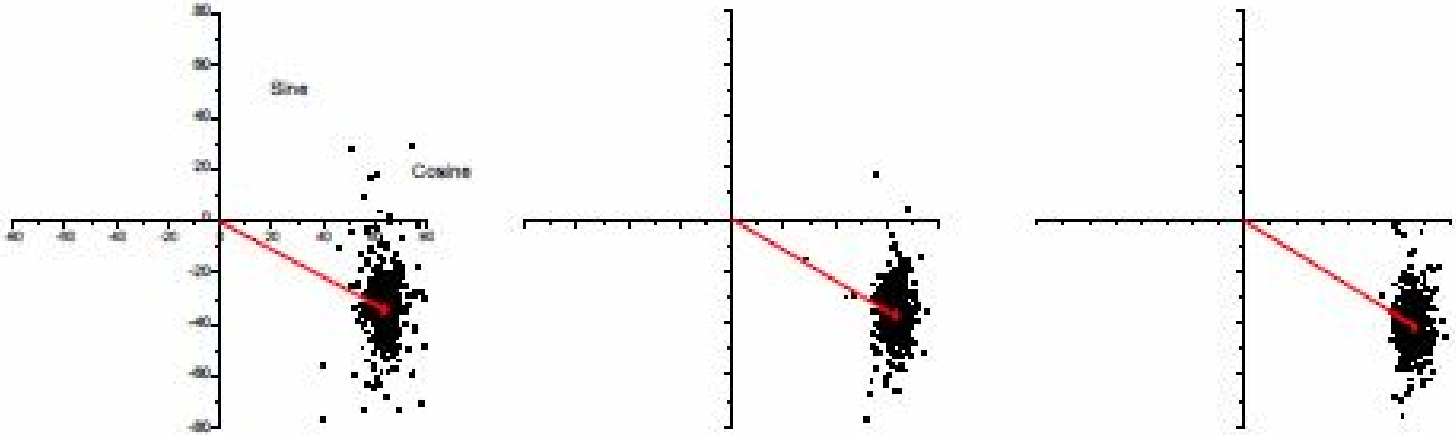

Scotopic Rod Response
400
200
0
Amplitude (μV)
0
100
200
Time (ms)
Normal
Patient


Scotopic Combined Response
Normal
Patient
200
0
-200
Amplitude (µV)
0
100
200
300
Time (ms)

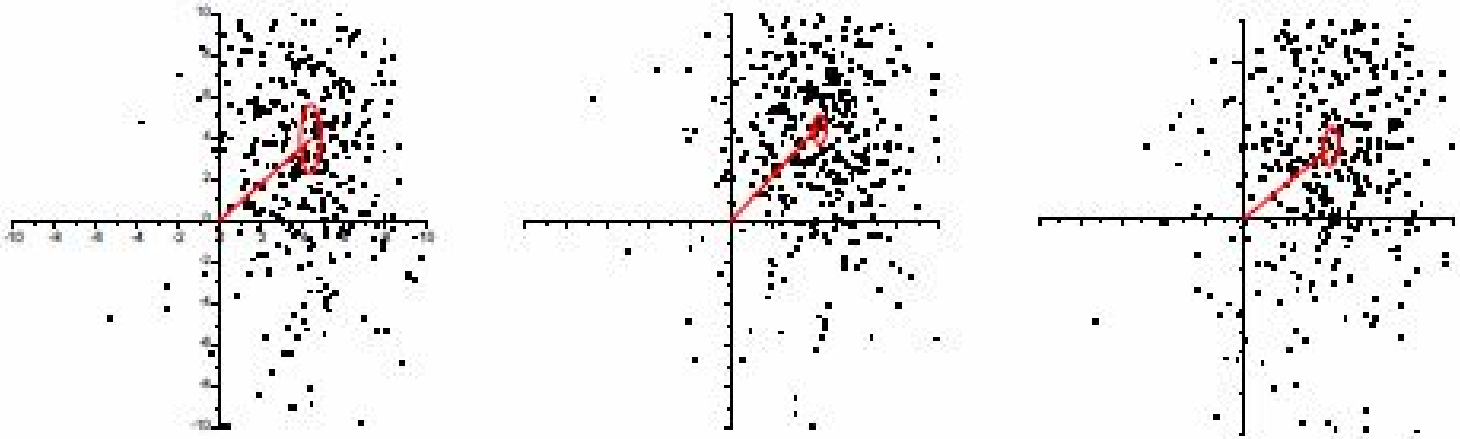

Photopic Response
Normal
Patient
Amplitude (µV)
150
100
50
0
-50
0
50
100
Time (ms)


Photopic 30 Hz Flicker
Normal
Patient
100
50
0
-50
Amplitude (μV)
0
50
100
150
Time (ms)

Control



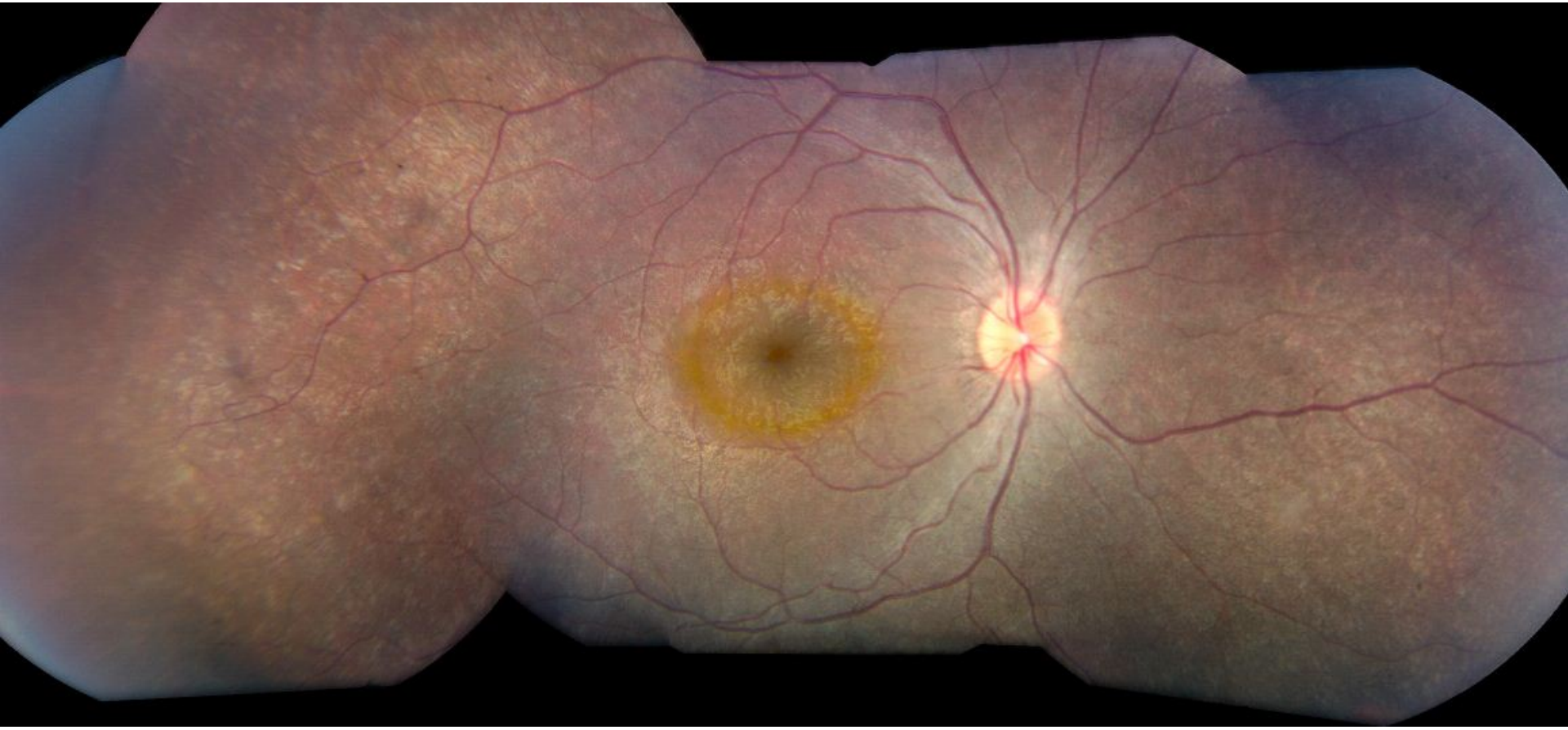
Usher type 1



Fundus Imaging Modalities

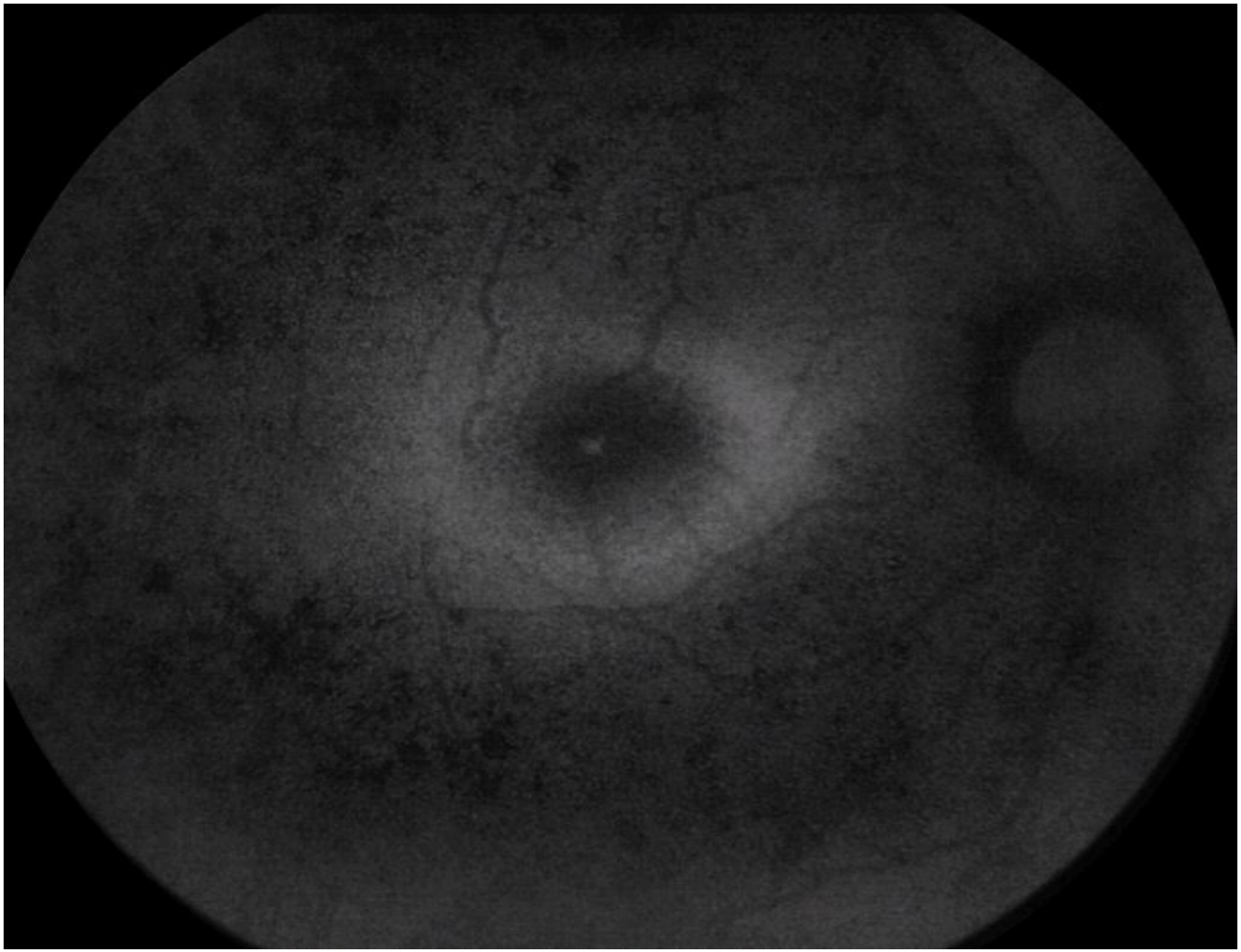
- Standard color fundus imaging is important and continues to be useful in documenting disease
- Newer modalities have established effectiveness as clinical diagnostic tools and might prove invaluable as clinical trial outcome measures:
  - Fundus autofluorescence
  - Wide-field imaging
- Optical coherence tomography has become indispensable as both a diagnostic and a clinical outcome measure tool

Right Fundus Color Imaging

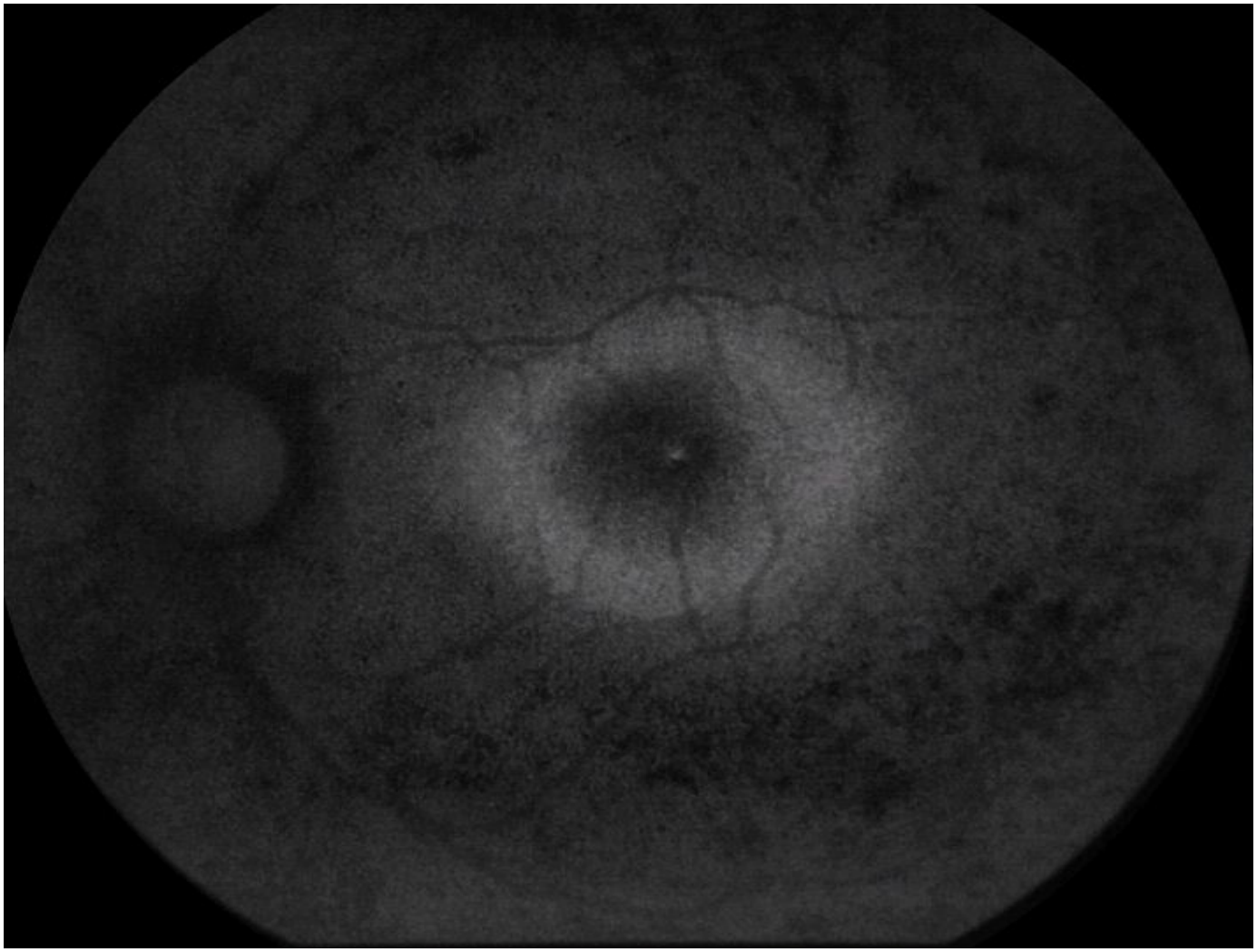


Left Fundus Color Imaging

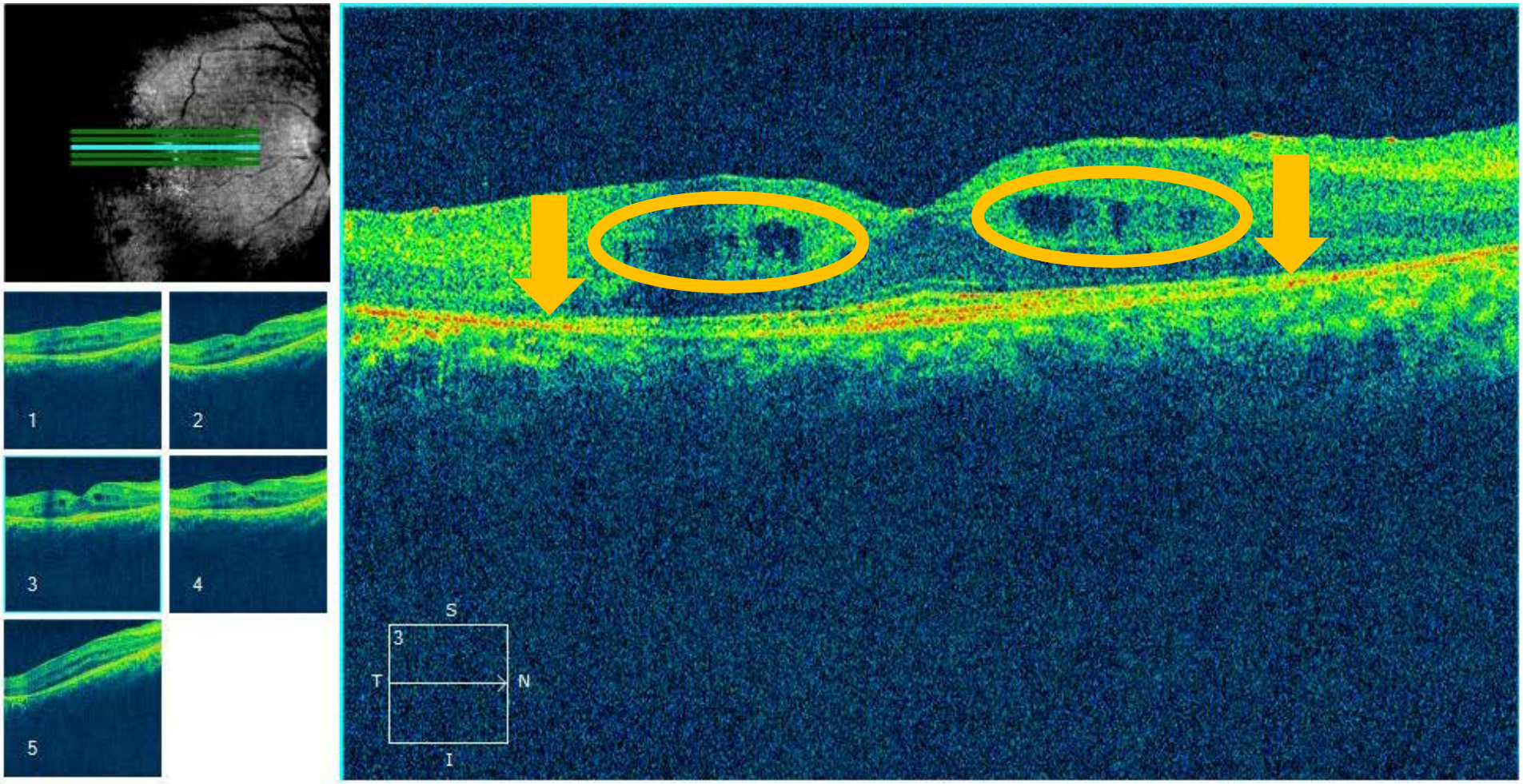
Right Fundus Autofluorescence



Left Fundus Autofluorescence

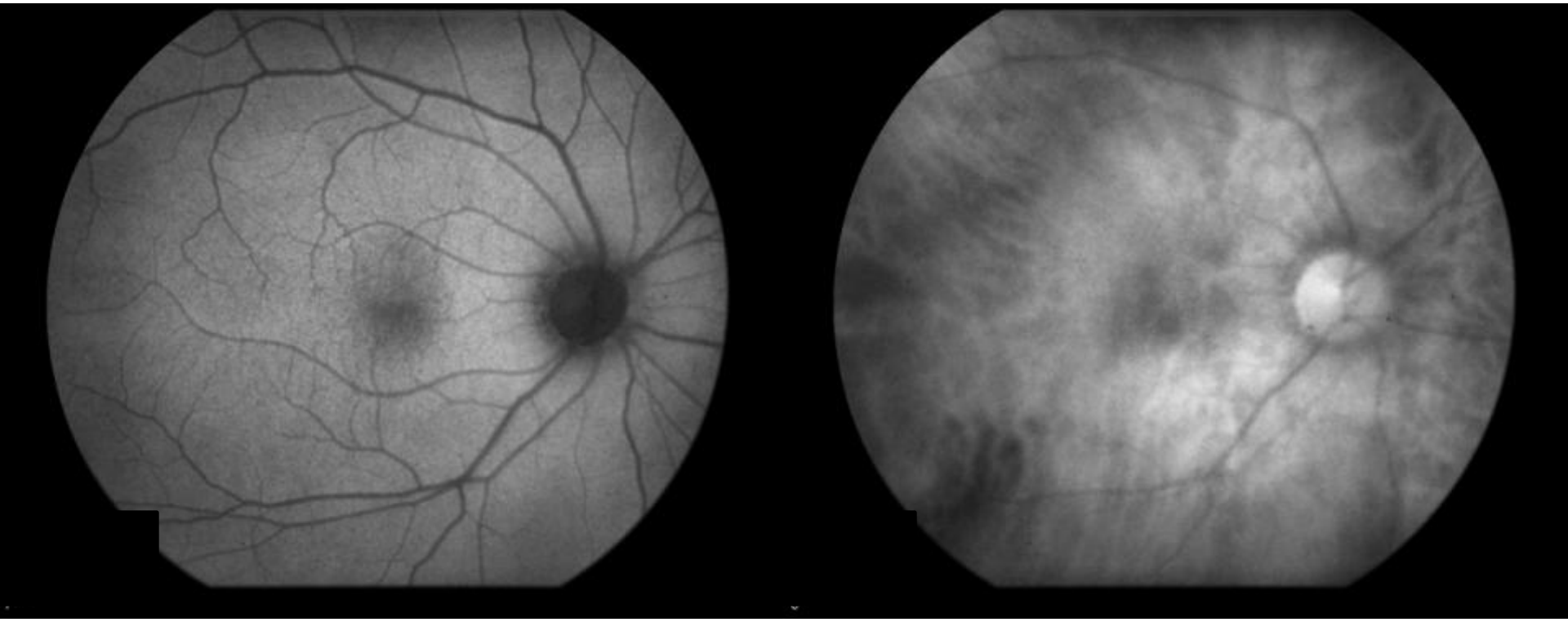


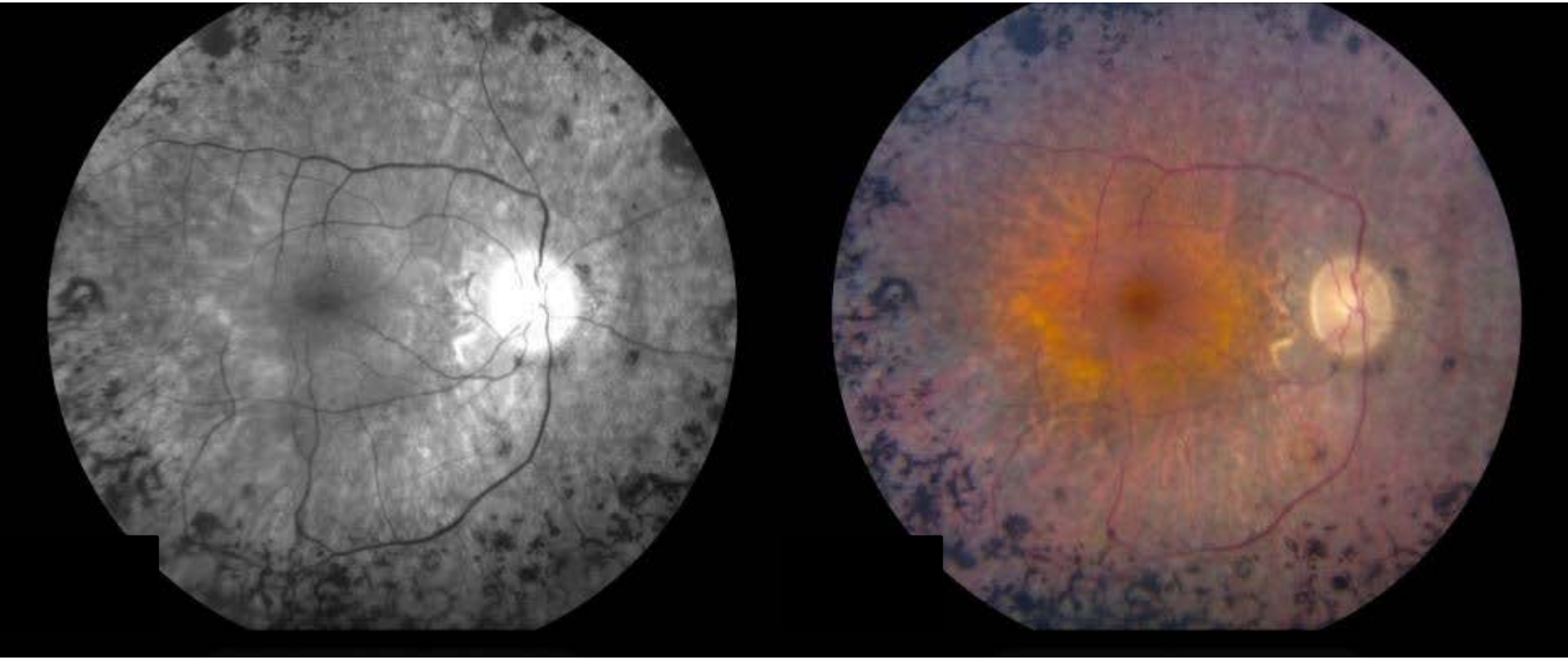
Right Macular Optical Coherence Tomography

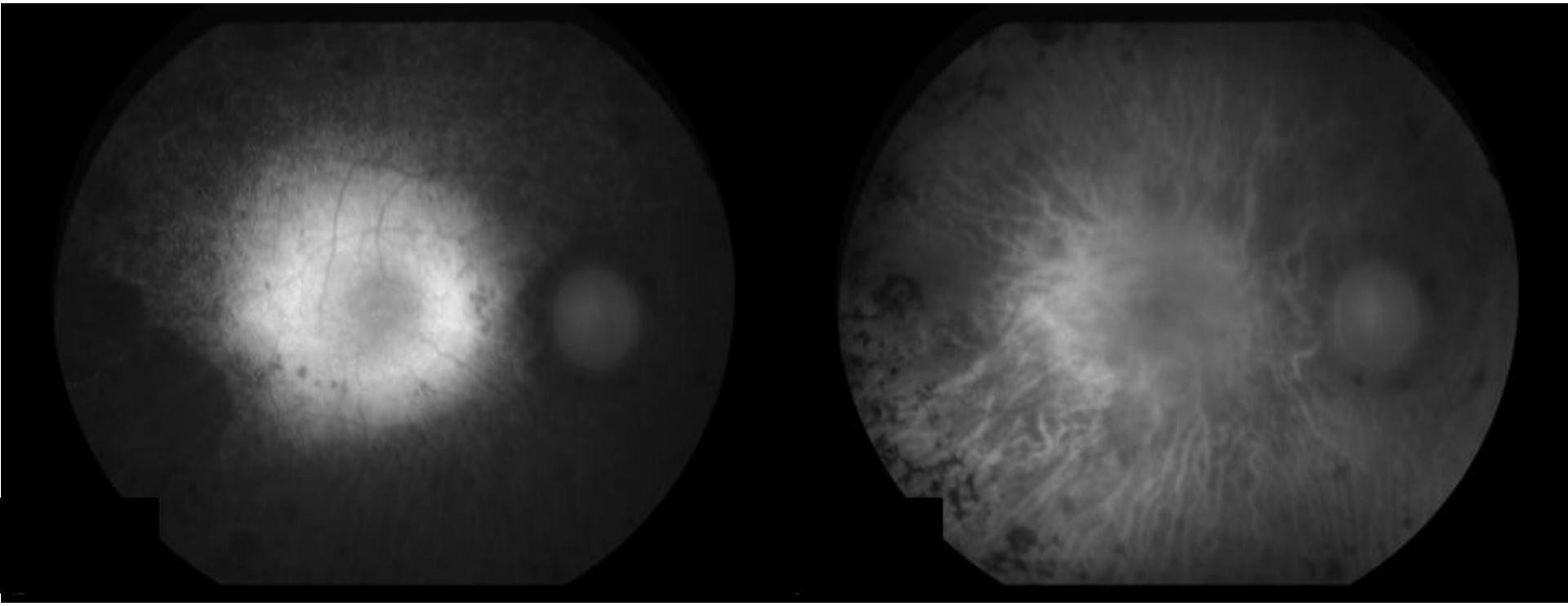


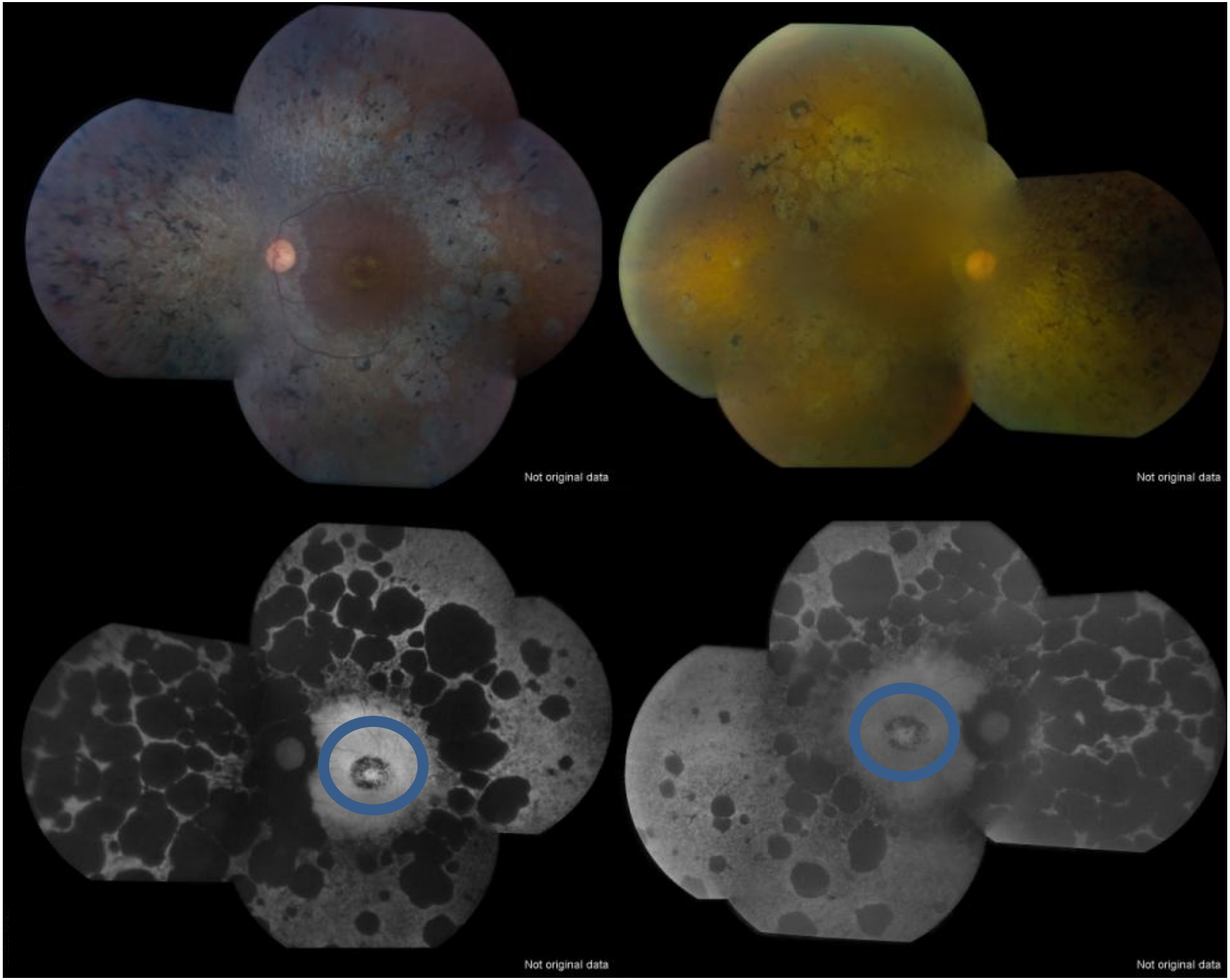
Unaffected 56 yo male

Unaffected 56 yo male





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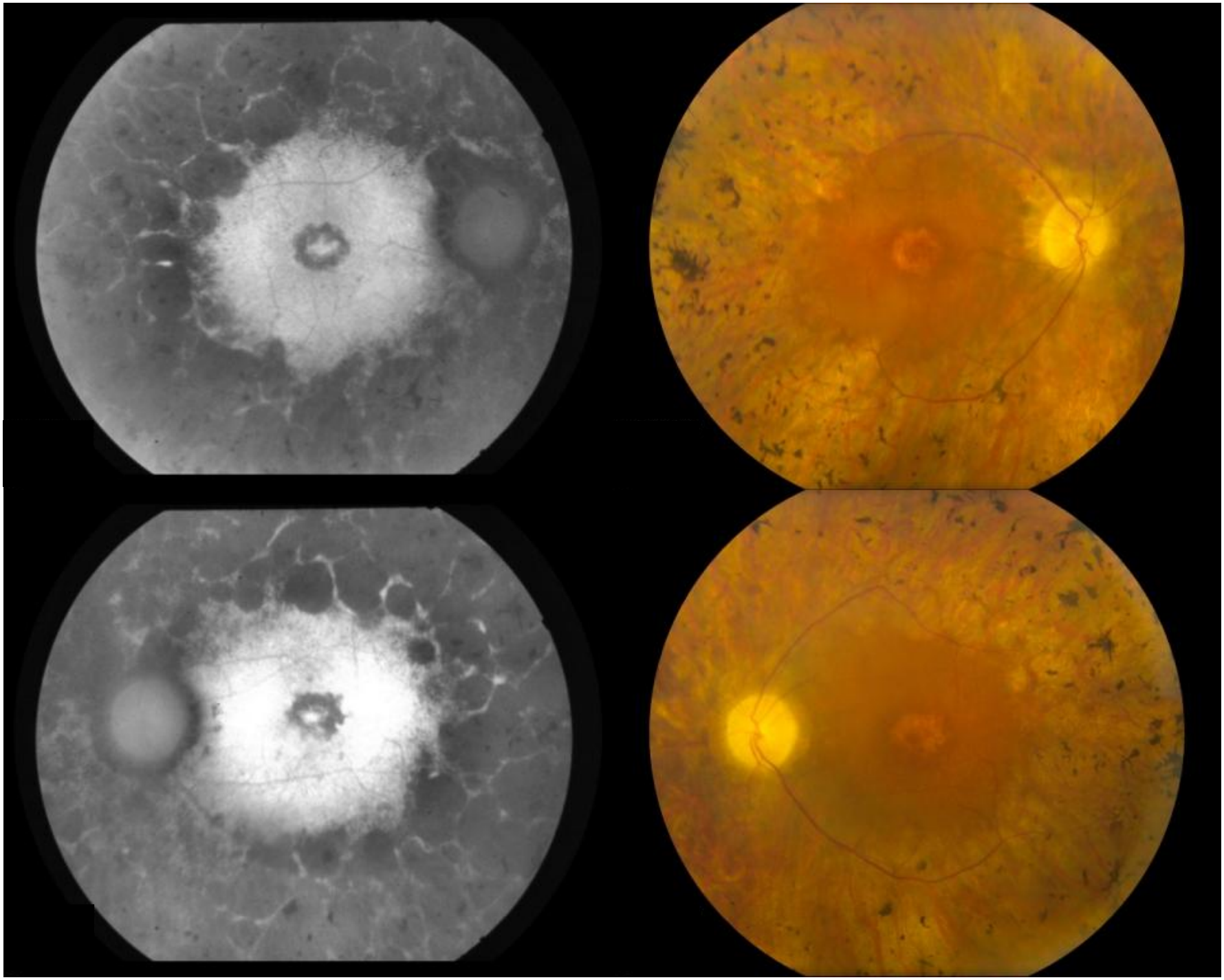

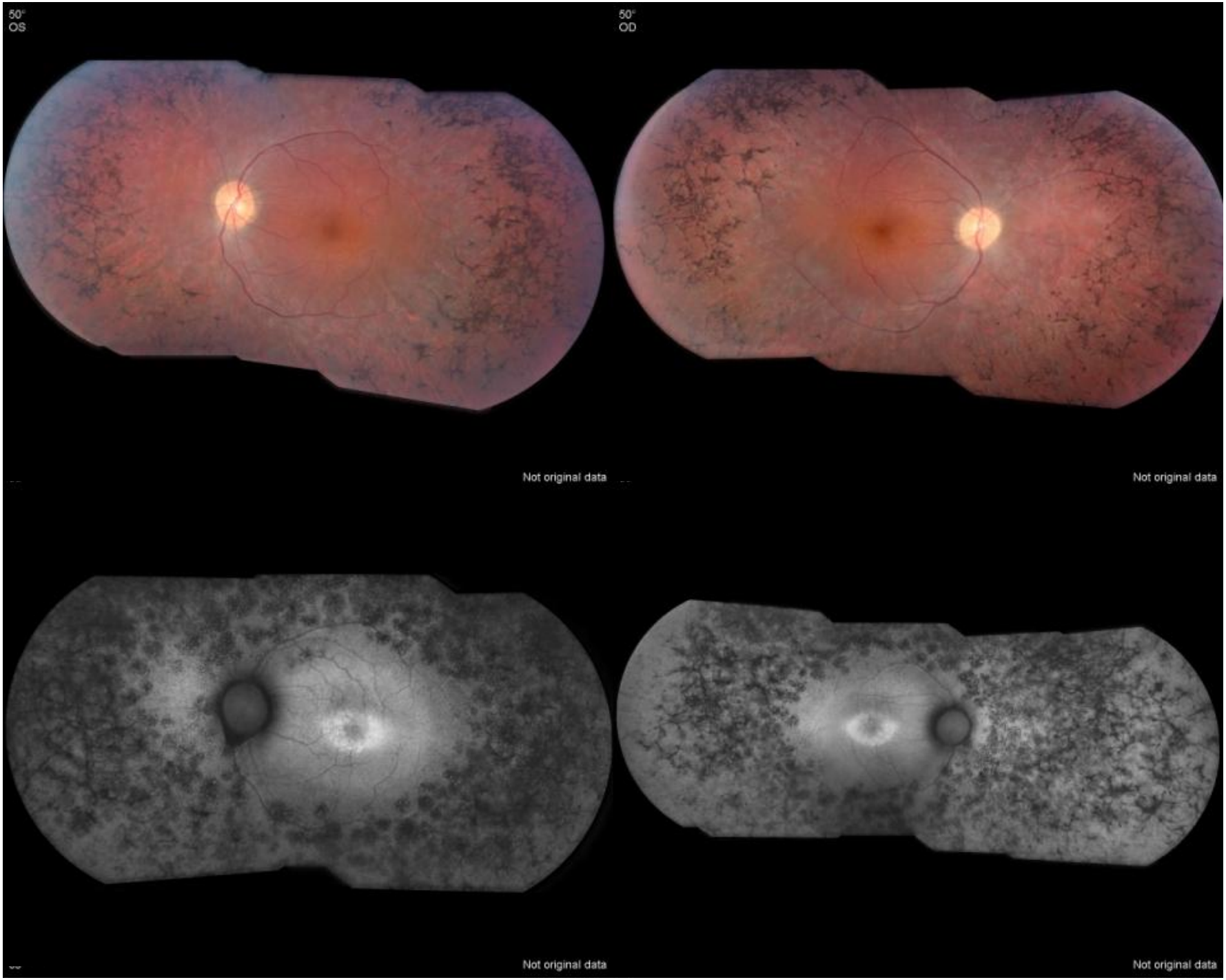
50°
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OD
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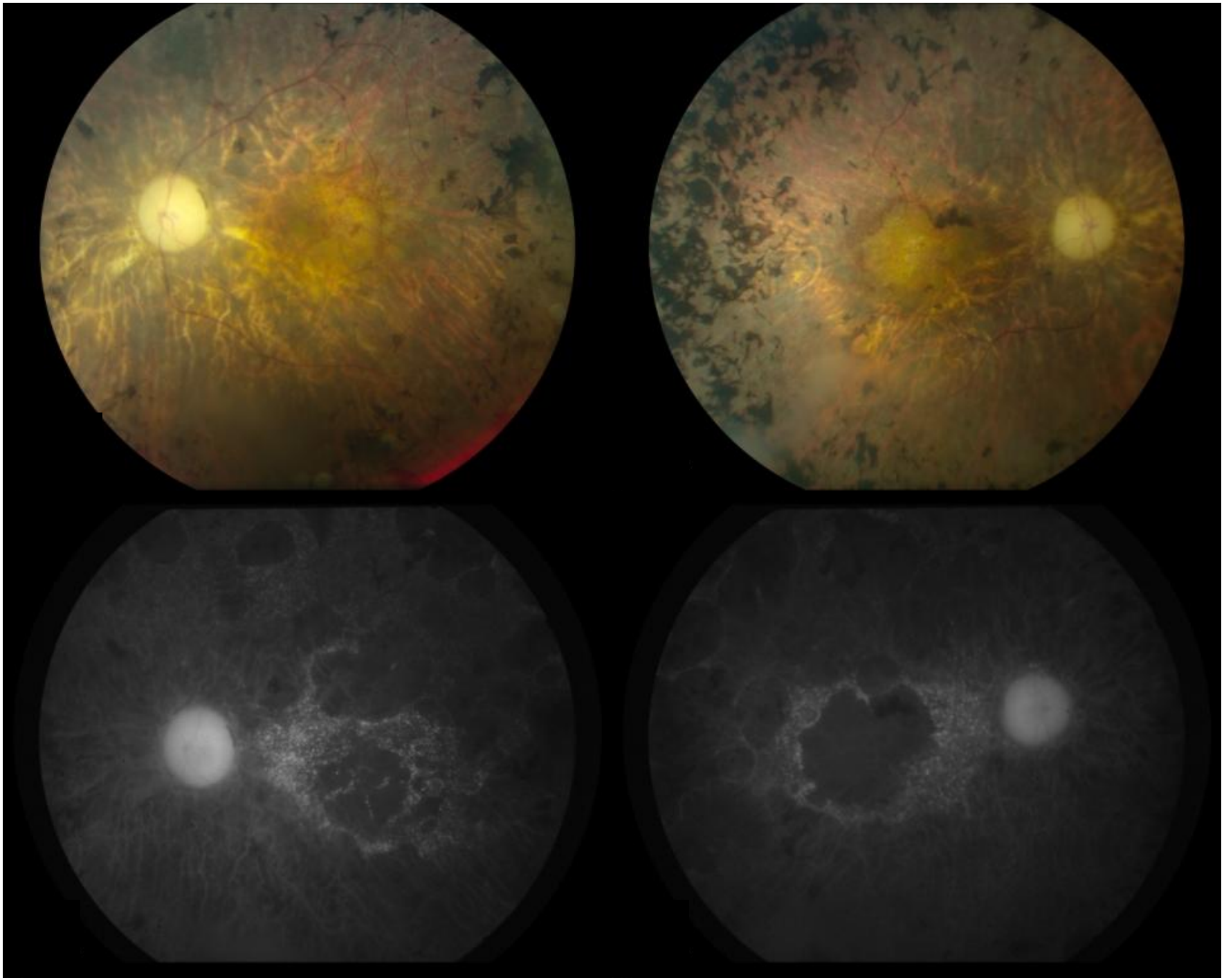
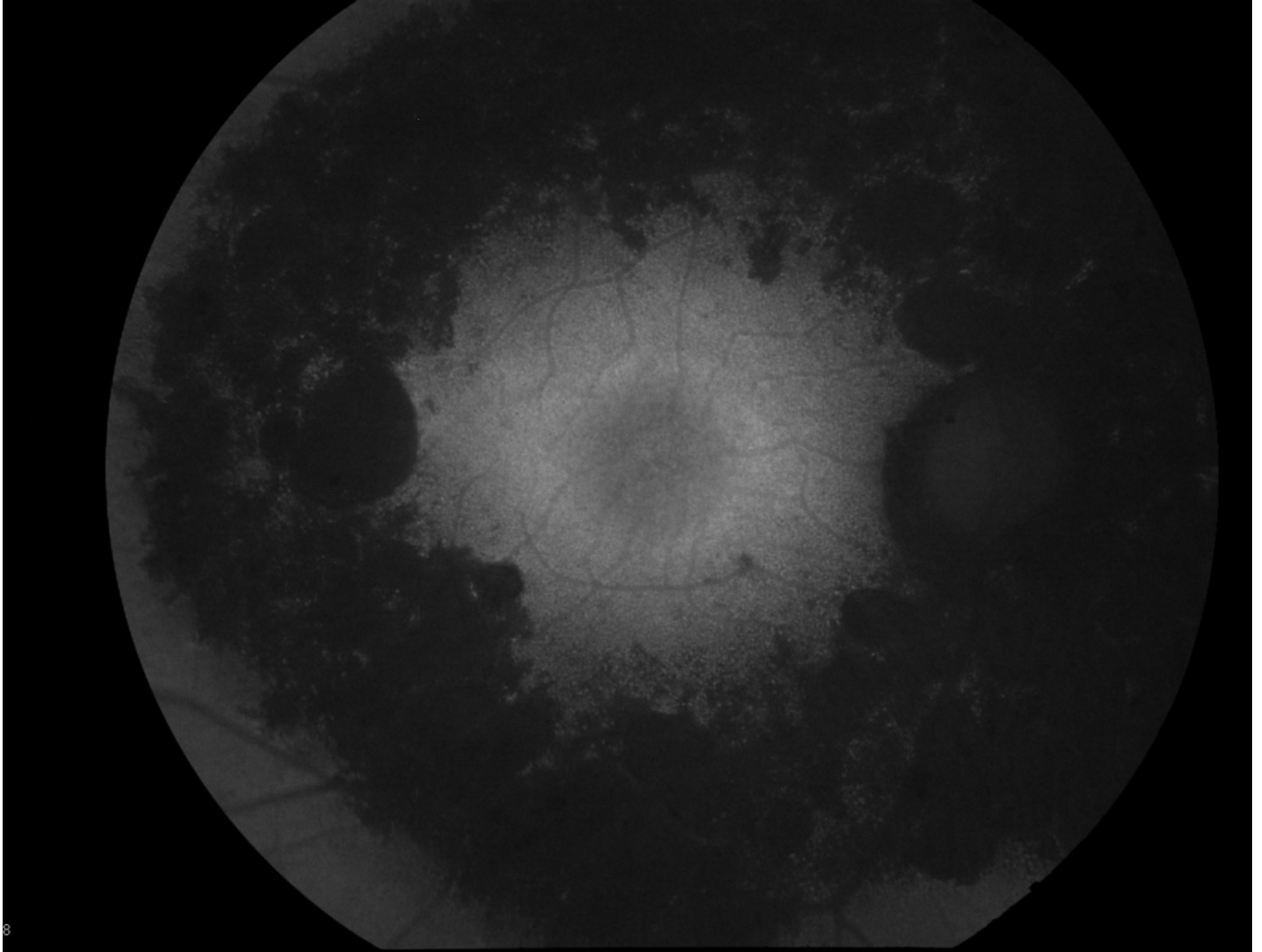


1

5

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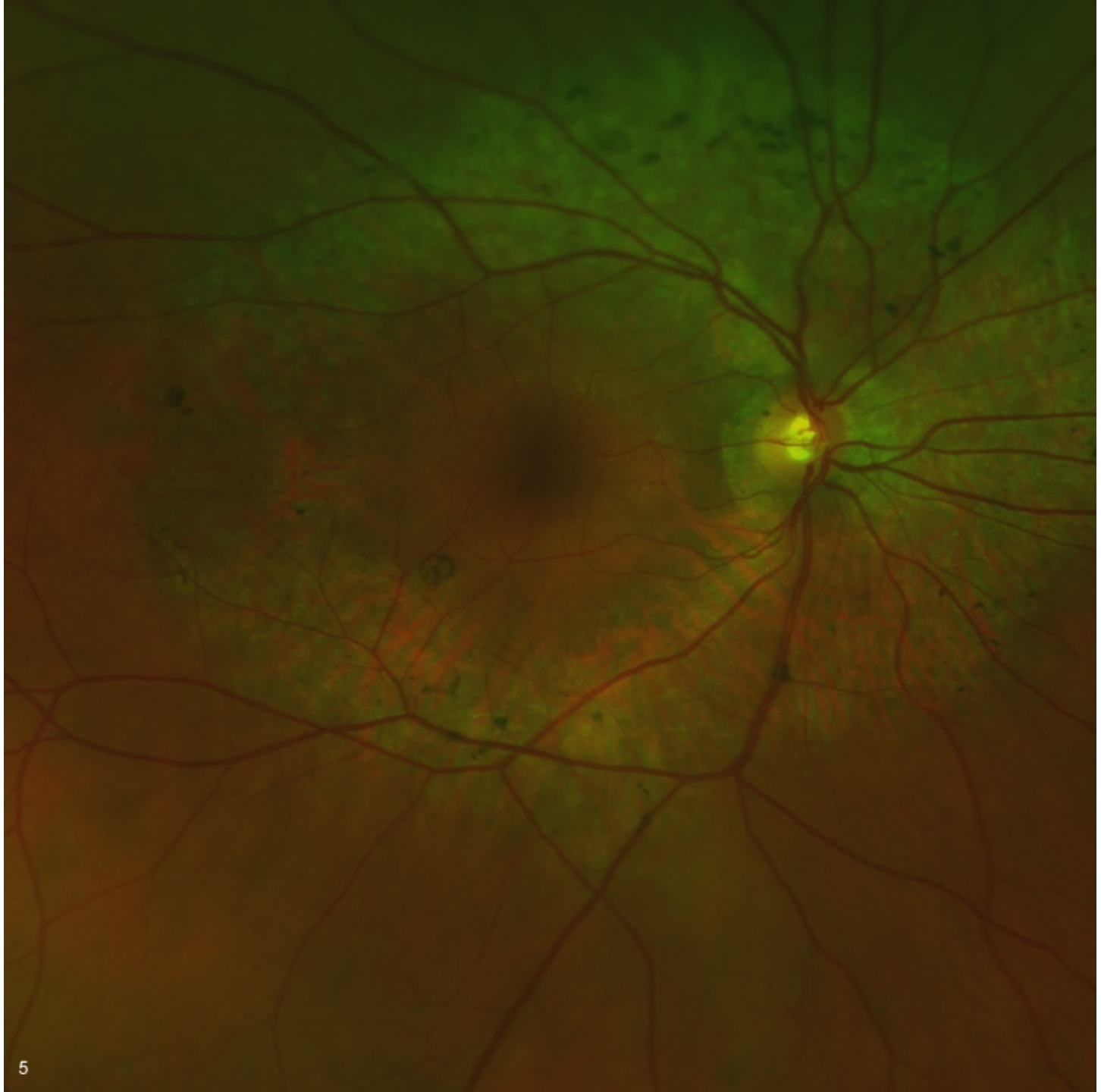

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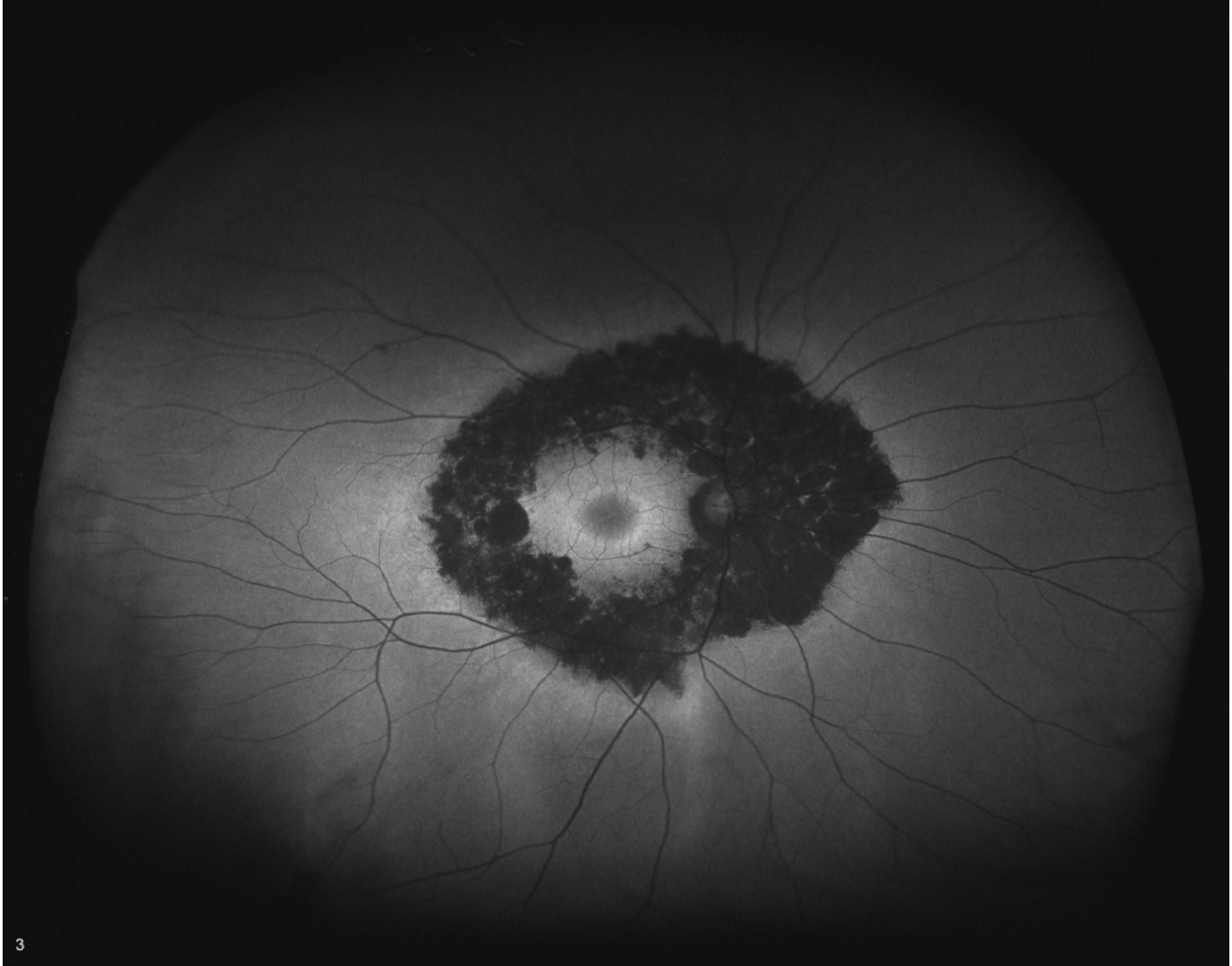

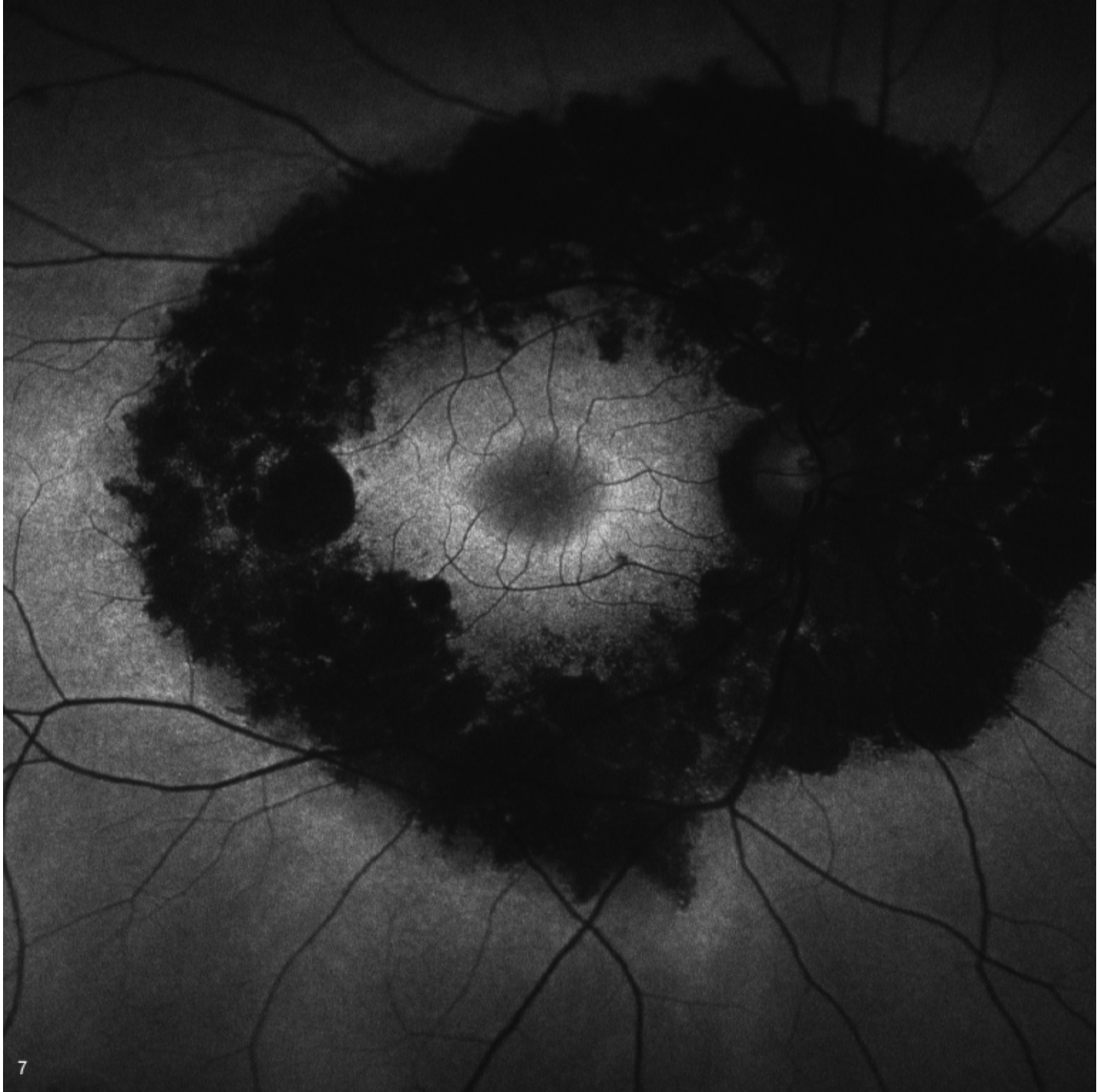

Conclusion

- Studies to investigate clinical findings in Usher syndrome are necessary
- A multidisciplinary approach with involvement of the ophthalmology, audiology / vestibular, genetic counseling, and molecular lab are needed
- Efforts at developing clinical trials would require robust animal models and a better understanding of disease outcome measures

Acknowledgements

- Thanks to the patients and their families.
- This effort is a collaboration involving a large group of people from the NEI, NIDCD, Queens College / CUNY, and HKNC. We are grateful to the referring physicians / health care teams.
- Special thanks to the team members and to NEI and NIDCD support:

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