Title: North Carolina Macular Dystrophy: 30-50-year follow-up of the original family

Authors: Kent W. Small, MD[1,2]; Fadi Shaya[1,2]; Jessica Avetisjan[1,2]; Nitin Udar, PhD[1]; Robert Wiggins, MD[3]

Affiliations:
1. Molecular Insight Research Foundation, Los Angeles, CA, United States.
2. Macula & Retina Institute, Glendale and Los Angeles, CA, United States.
3. Asheville Eye Associates, NC, United States

Financial Disclosures

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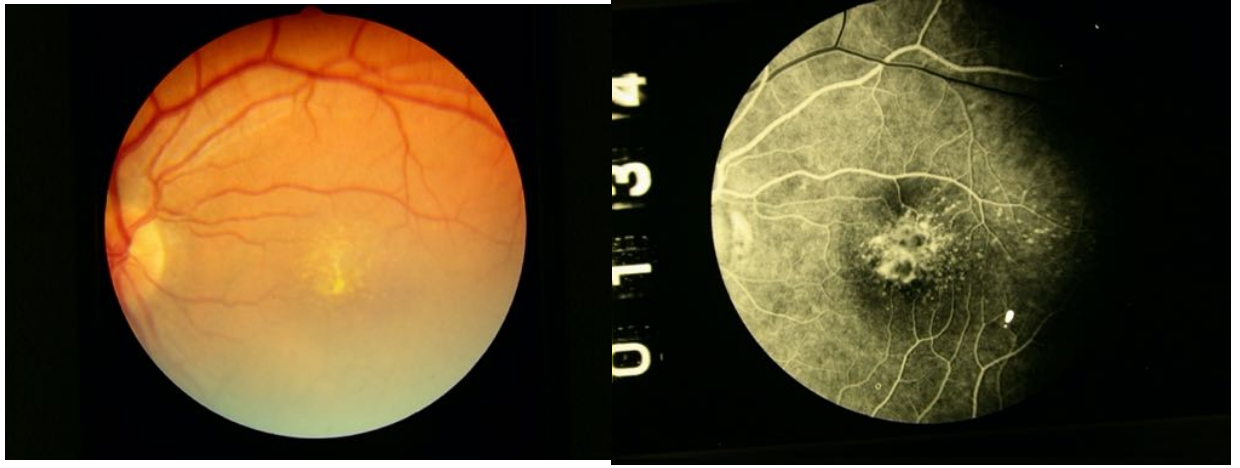
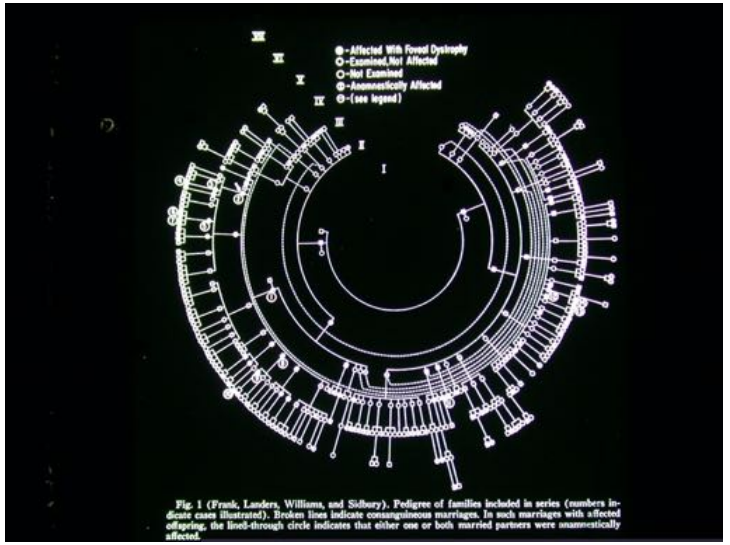
Summary



- 25 subjects re-examined
- From original NCMD family (family 765)
- The point mutation CHR6: 99593030 (Hg38) in a non-coding region of a DNASE1 hypersensitivity binding site on chromosome 6 (MCDR1) in all affected subjects
- One of the features of NCMD is the lack of progression in an individual
- Most NCMD patients have stable vision and fundus findings up to 50 years follow-up
- The ones who lost vision did so with NCMD grade 2 disease
  - developed choroidal neovascularization
- Only patients with grade 2 NCMD seem to be at risk for further / progressive vision loss
- With anti-VEGFs now available, some of these patients may benefit from these treatments

Introduction



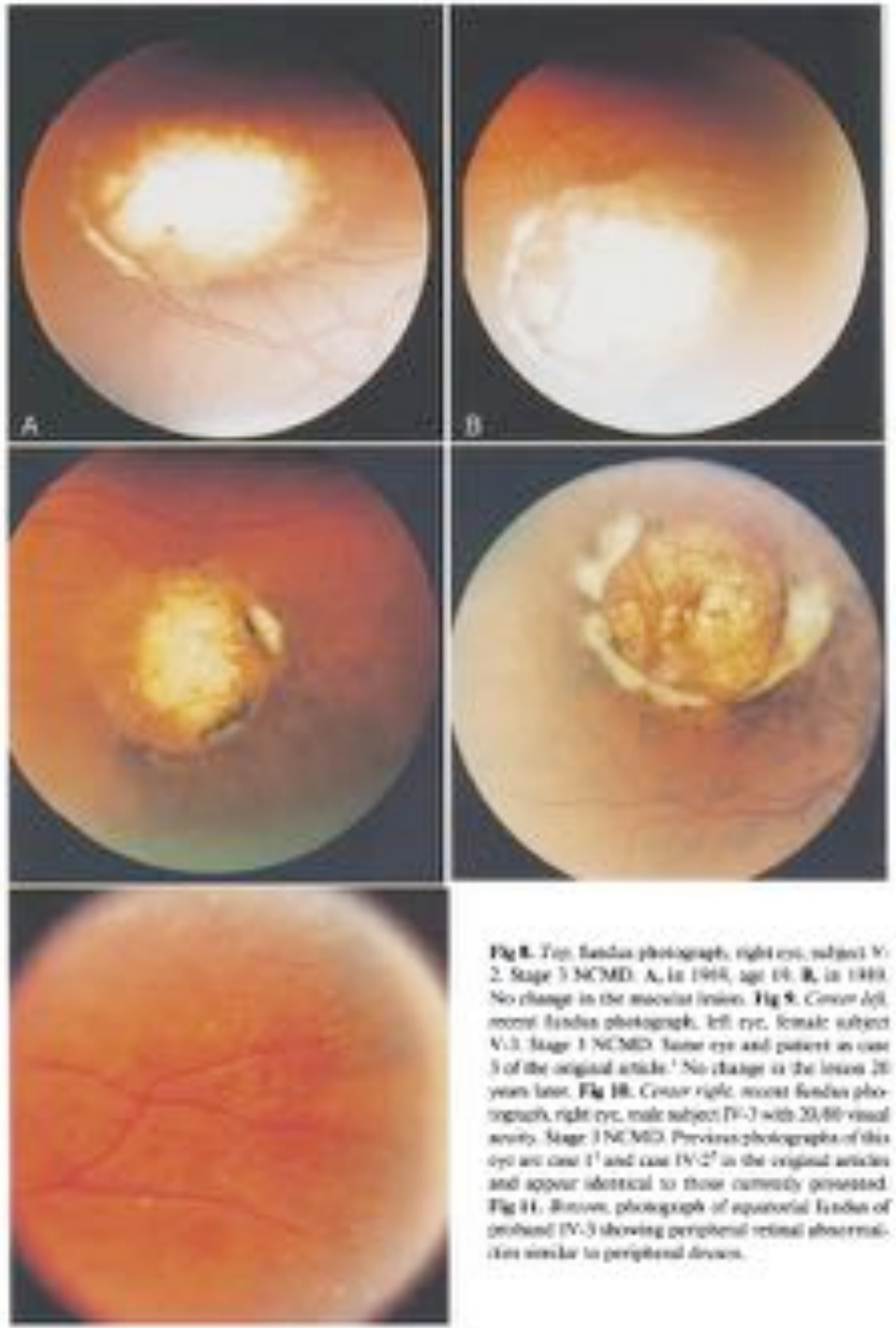
- The clinical phenotype of NCMD is
  - highly variable
  - remains poorly appreciated and understood
- One feature of NCMD is the **lack of progression**
- Original Lefler, Wadsworth and Sidbury Syndrome
- named it “dominant **progressive** foveal dystrophy” 1971

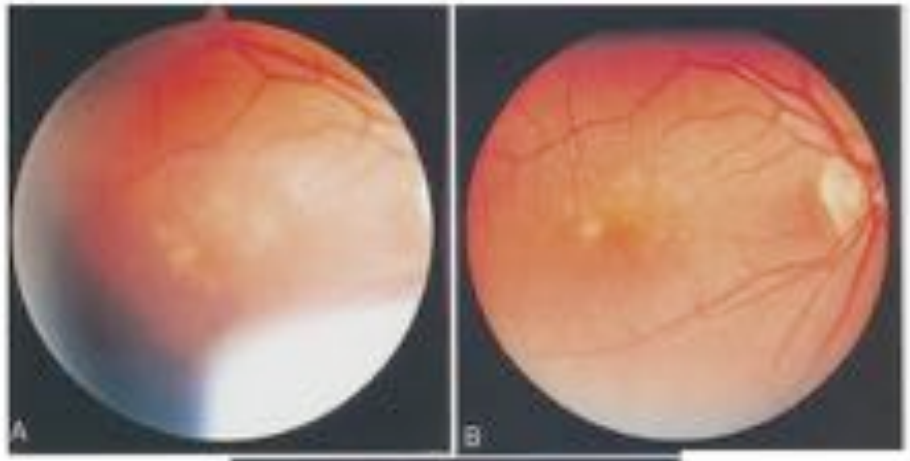
North Carolina Macular Dystrophy, Revisited

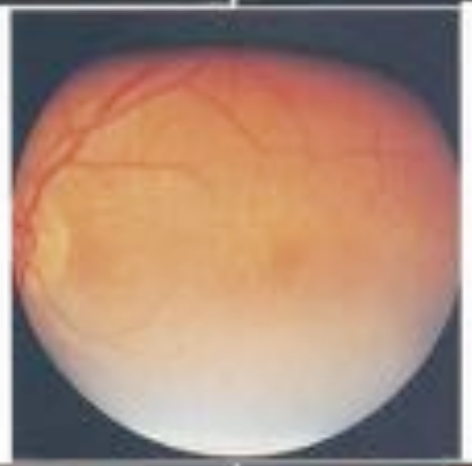
KENT W. SMALL, MD

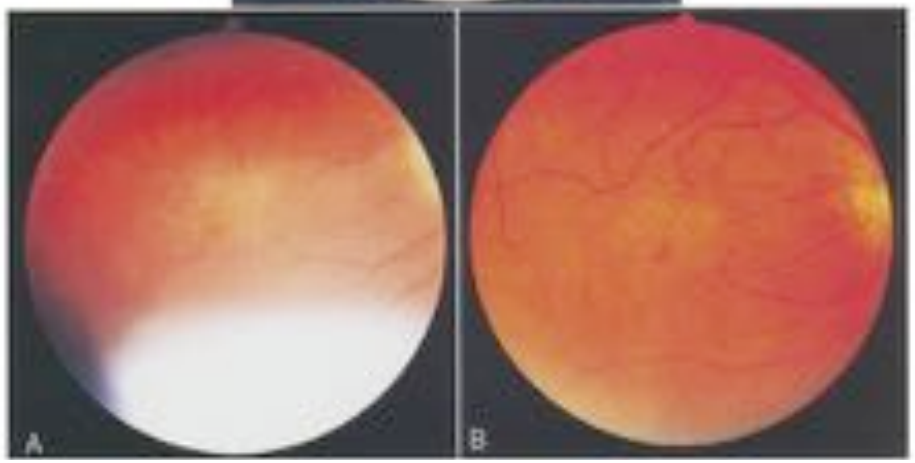
Abstract: Progression of the maculopathy in North Carolina macular dystrophy (NCMD) was not well documented. Thus, the author recently examined 22 affected members of the original kindred. Evidence of progression of the macular disease was sought through comparison of the recent fundus findings with old fundus photographs and from subjective complaints of worsening visual acuity. Only 1 of the 22 affected subjects had evidence of such change. Additionally, two new findings of NCMD were observed: (1) severe macular lesions which were staphylomatous or excavated in appearance, not flat, and atrophic as previously described; and (2) peripheral retinal drusen variably present in affected subjects, in contrast to the "normal peripheral retina" originally described. These new findings, along with the generally stable course of the disease would seem to alter our understanding of the relationship of NCMD to other dominant macular dystrophies. *Ophthalmology 96:1747–1754, 1989*

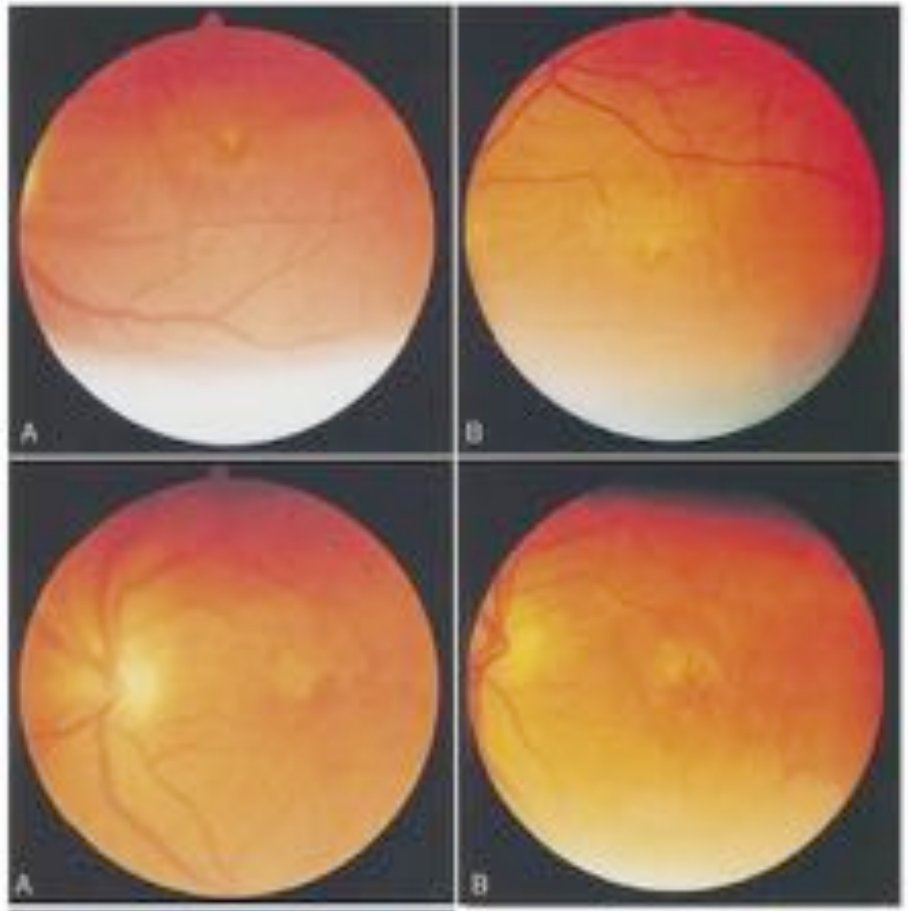
autosomal dominant
congenital
completely penetrant
non-progressive (except CNVMs)
macular malformation
Marked variable expressivity,
- drusen,
- confluent drusen ,
- fibrosis,
- coloboma – like lesion











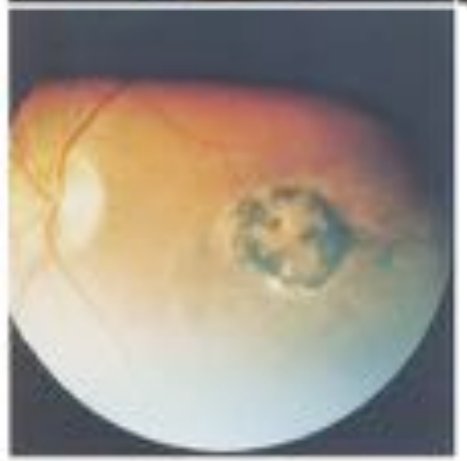
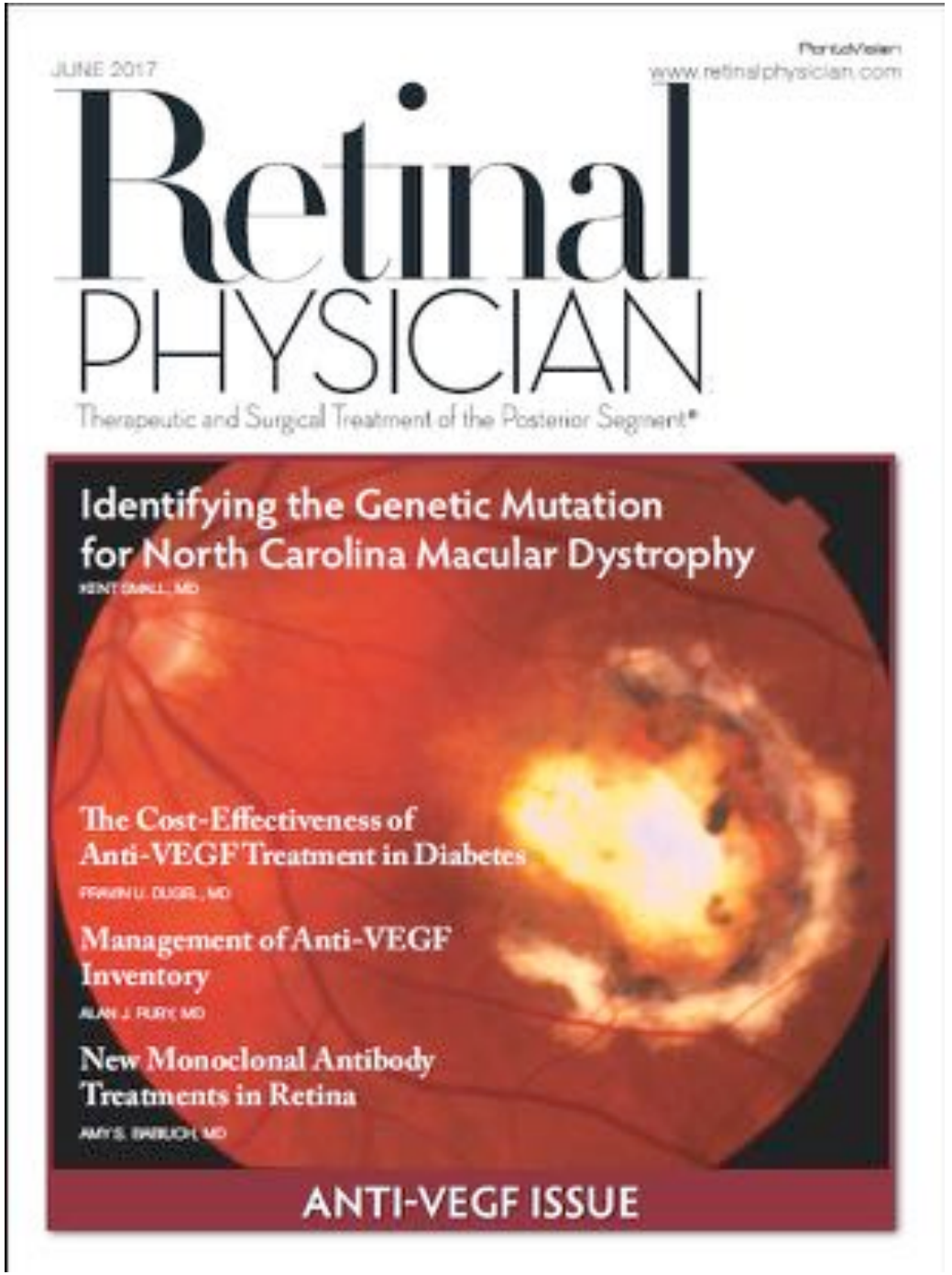


Fig 5. *Eye*, fundus photographs, left eye, subject V-6. Bilateral symmetry in stage 1 NCMD. **A**, photograph from 1969. **B**, photograph from 1989. No change in stage 1 macular disease. **Fig 6.** *Center*, fundus photographs, left eye, female subject IV-6. Stage 1 NCMD. **A**, in 1969. **B**, in 1989. No change in macular lesion. **Fig 7.** *Bottom*, fundus photograph, left eye, female subject VI-6, age 35, with 20/80 visual acuity; severe stage 2 NCMD. Significant change seen on comparison with case 6 in the original article.[1]

NCMD is worldwide

- NCMD has been found worldwide in
- over 50 families by one investigator (KWS)
- Families have been reported in the
- United States,
- Europe, (eastern and western)
- Central America (Belize)
- Australia
- New Zealand
- Korea
- China
- **“North Carolina macular dystrophy” is a gross misnomer**



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Multimodal Imaging and Functional Testing in a North Carolina Macular Disease Family: Toxoplasmosis, Fovea Plana, and Torpedo Maculopathy Are Phenocopies

Kent W. Small, MD,[1,2] Elaine M. Tran, BS,[3] Leslie Small, OD,[4] Rajesh C. Rao, MD,[5,6,7,8,9] Fadi Shaya, BS[1,2]

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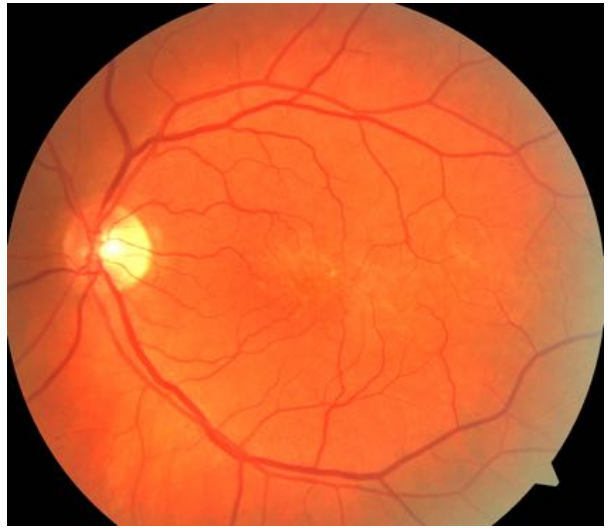
Case report

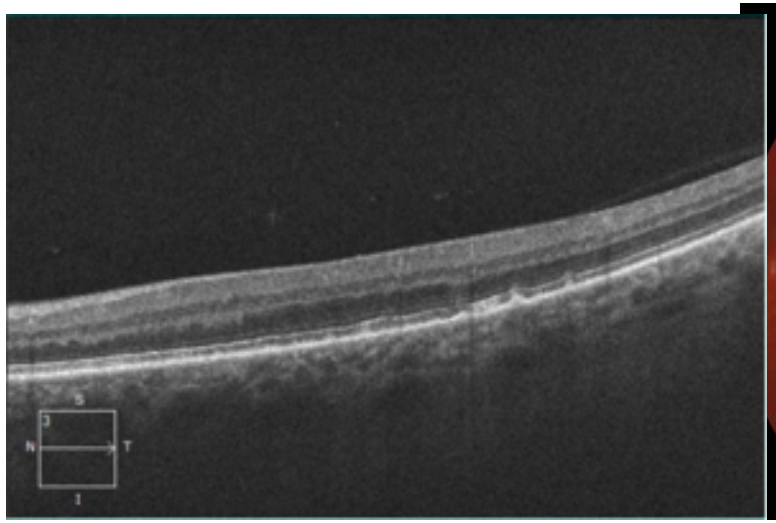
Congenital toxoplasmosis as one phenocopy of North Carolina Macular Dystrophy (NCMD/MCDR1)

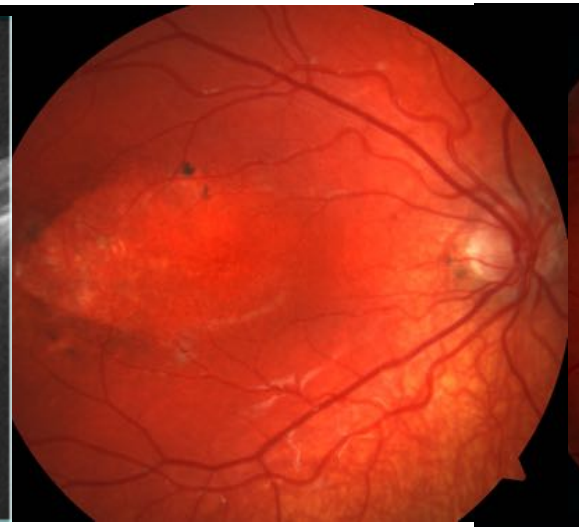
Kent W. Small (MD)[a,b,*], Andrea L. Vincent (MBChB, MD)[c,d], Chelsey L. Knapper (MD)[a,b], Fadi S. Shaya (BS)[a,b]

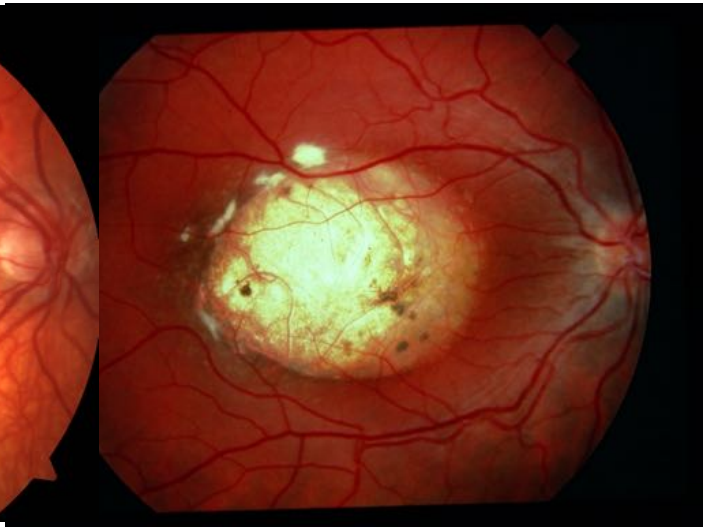
[a] Macula and Retina Institute, Los Angeles and Glendale, California, USA
[b] Molecular Insight Research Foundation, Los Angeles and Glendale, California, USA
[c] Ophthalmology, New Zealand National Eye Centre, University of Auckland, New Zealand
[d] Eye Department, Greenlane Clinical Centre, Auckland District Health Board, Auckland, New Zealand

- AMD (drusen)
- Torpedo maculopathy
- Congenital Toxoplasmosis
- Fovea plana









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North Carolina Macular Dystrophy Is Caused by Dysregulation of the Retinal Transcription Factor *PRDM13*

Kent W. Small, MD,[1] Adam P. DeLuca, PhD,[2] S. Scott Whitmore, PhD,[2] Thomas Rosenberg, MD,[3] Rosemary Silva-Garcia, MD,[1] Nitin Udar, PhD,[1] Bernard Puech, MD,[4] Charles A. Garcia, MD,[5] Thomas A. Rice, MD,[6] Gerald A. Fishman, MD,[7] Elise Héon, MD,[8] James C. Folk, MD,[2] Luan M. Streb, BA,[2] Christine M. Haas, BA,[2] Luke A. Wiley, PhD,[2] Todd E. Scheetz, PhD,[2] John H. Fingert, MD, PhD,[2] Robert F. Mullins, PhD,[2] Budd A. Tucker, PhD,[2] Edwin M. Stone, MD, PhD[2]

Initial publication of mutations 11 families

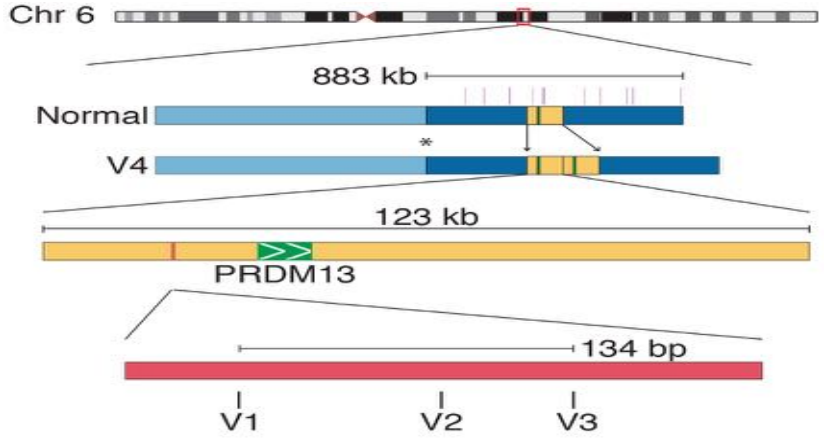
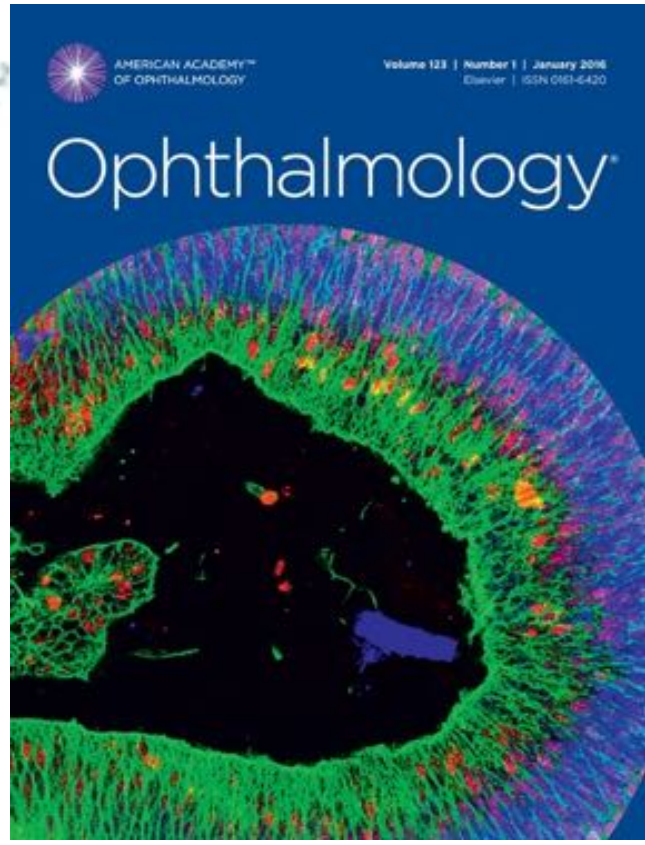
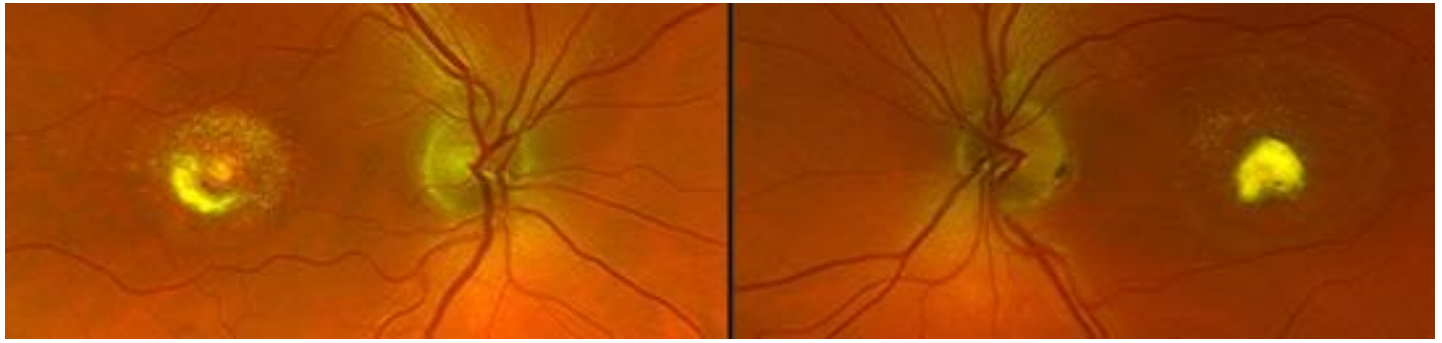


Figure 2



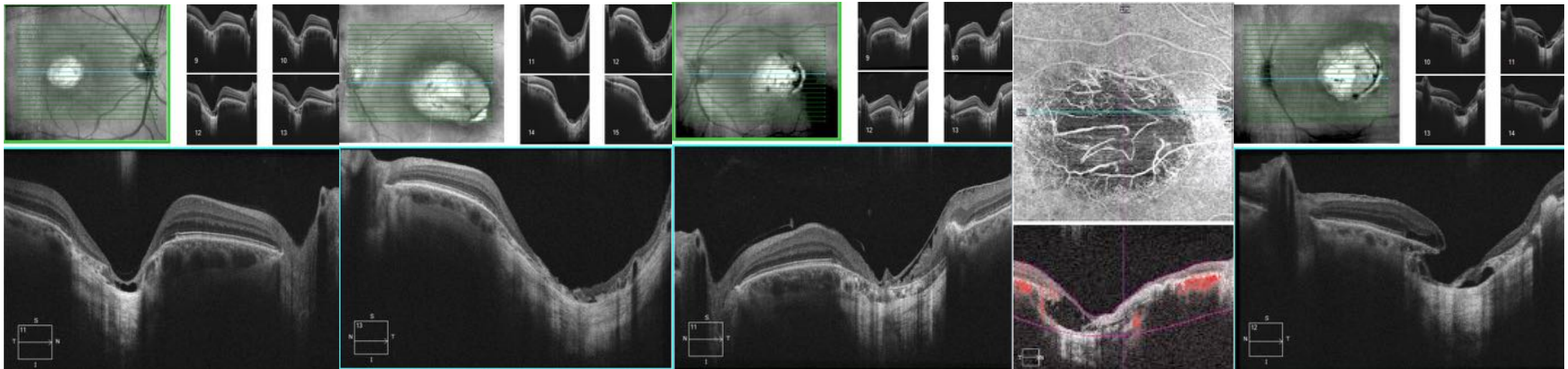
Methods

- 25 affected subjects of the original NCMD pedigree
- recently re-examined by KS in an office setting
- Evaluation on all affected subjects included:
  - Standard Snellen visual acuity
  - Slit lamp examination, 90 D and 20 D fundus examinations
  - Fundus photography (OPTOS California; Marlborough, MA)
  - SD-OCT (Zeiss Cirrus 5000; Oberkochen, Germany)
- findings were compared with the original data collected by KS in 1988 and images from 1971 by Lefler (HL) et al.
- SD-OCT was not available original ascertainment of the family in 1988
- Blood was collected for DNA extraction and analysis
- IRB approval and signed consent was obtained on all participating subjects



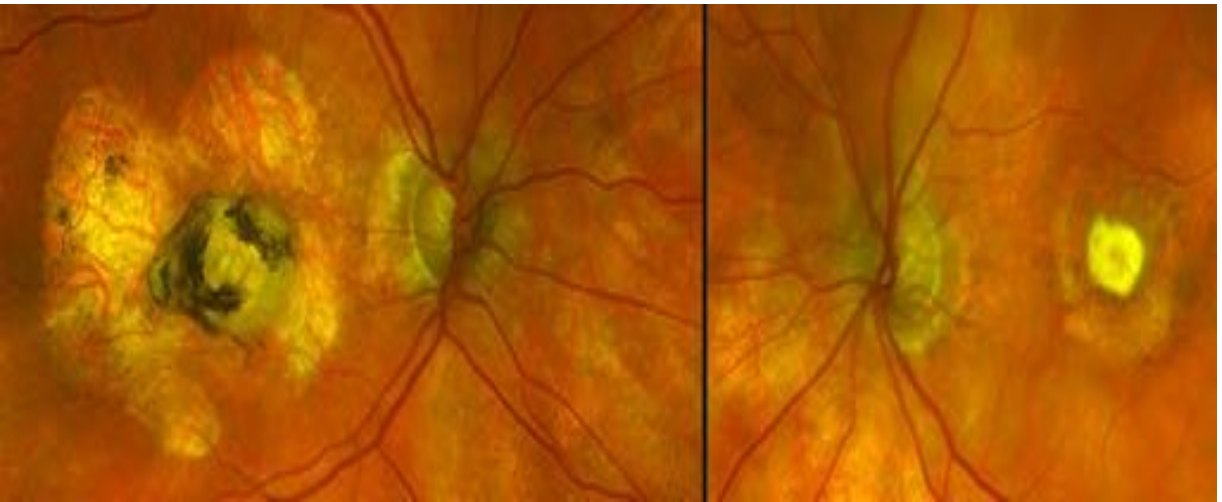
Results

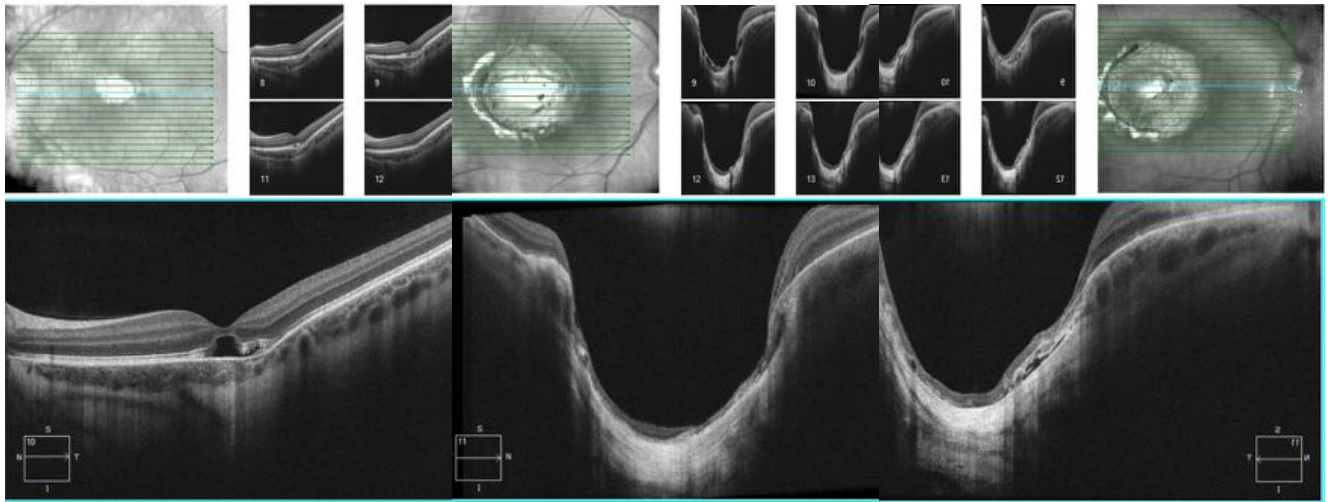
- The 25 subjects examined were part of the original NCMD family (family 765)
- The point mutation CHR6: 99593030 G>C (Hg38) was found
- in a non-coding region of a DNASE1 hypersensitivity binding site on chromosome 6 MCDR1 in all affected subjects
- 8 were affected children of those originally examined



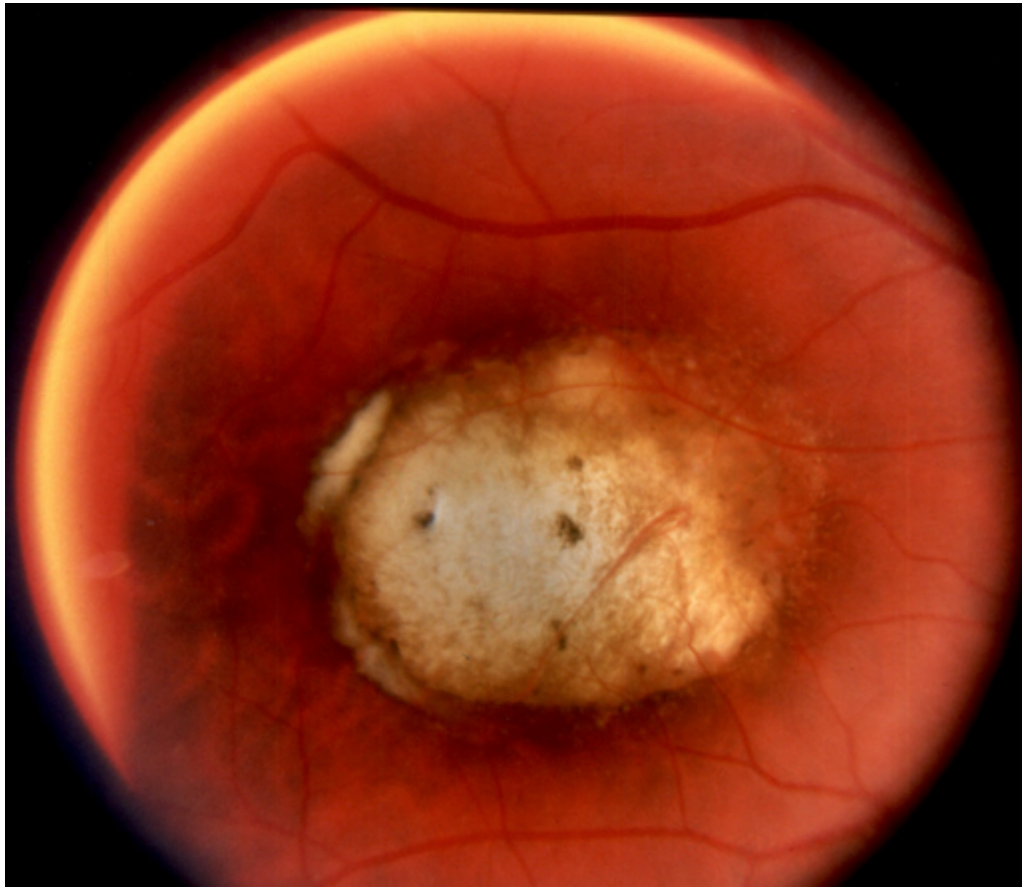
RESULTS

- 17 subjects (34 eyes) had been examined 30-50 years previously
- 6 previously examined by Lefler 50 years ago and fundus photos published in 1971
- Out of those 17 subjects (34 eyes):
- 4 (11%) eyes showed worsening of vision
- with fundus photos showing evidence of fibrosis from CNVM
- Some have surrounding atrophy: resolved subretinal fluid
- 1 unexplained improvement in VA

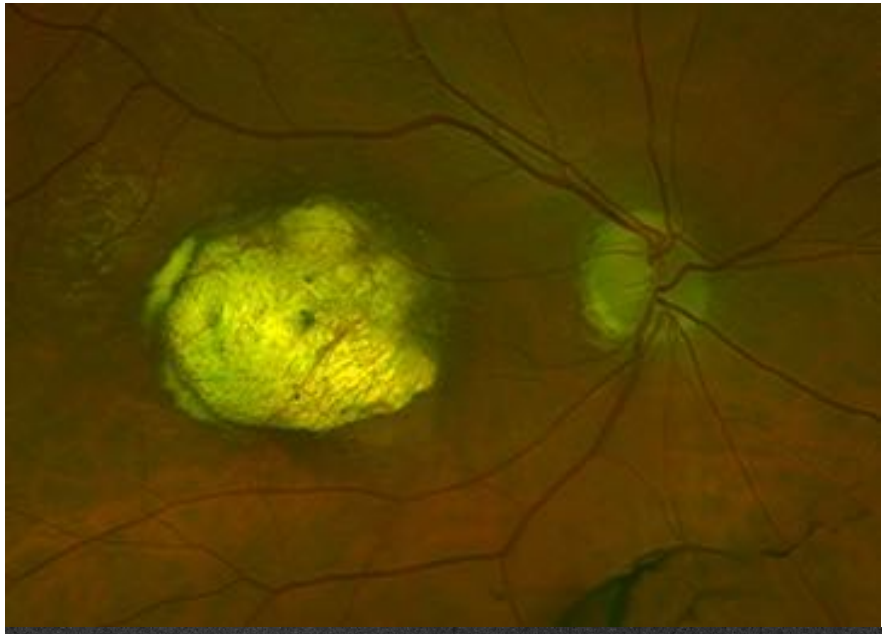


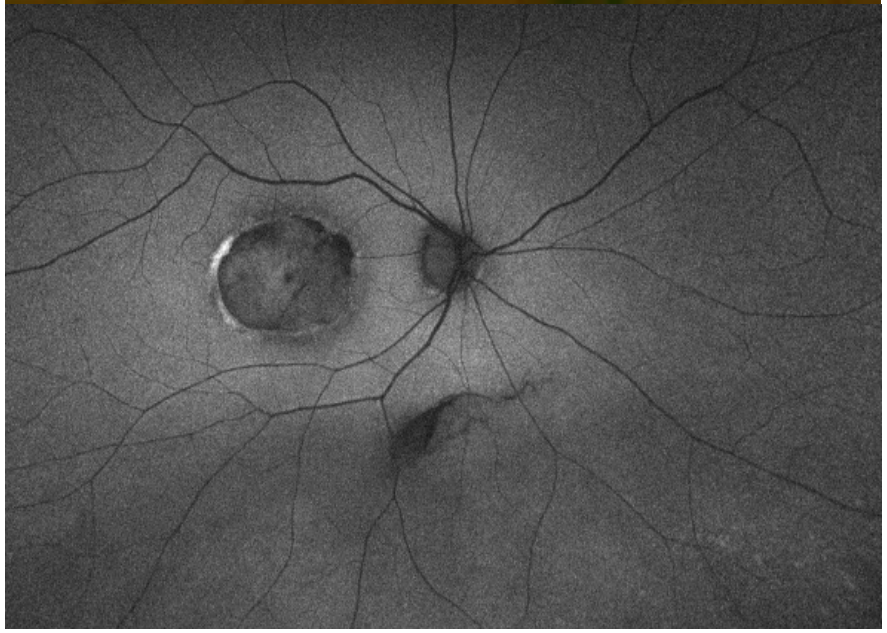


Patient 2 at 29 years old
NCMD grade 3
VA: 20/40 OD

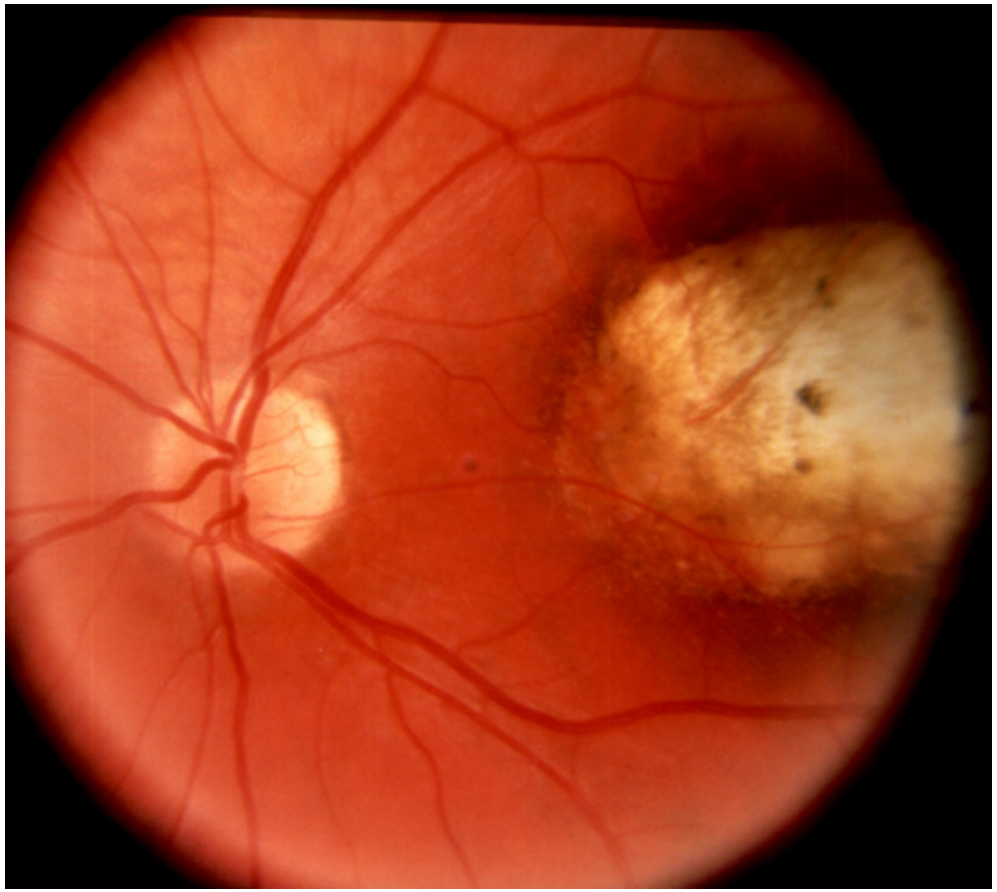


Patient 2 at 60 years old NCMD grade 3
VA: 20/40 OD

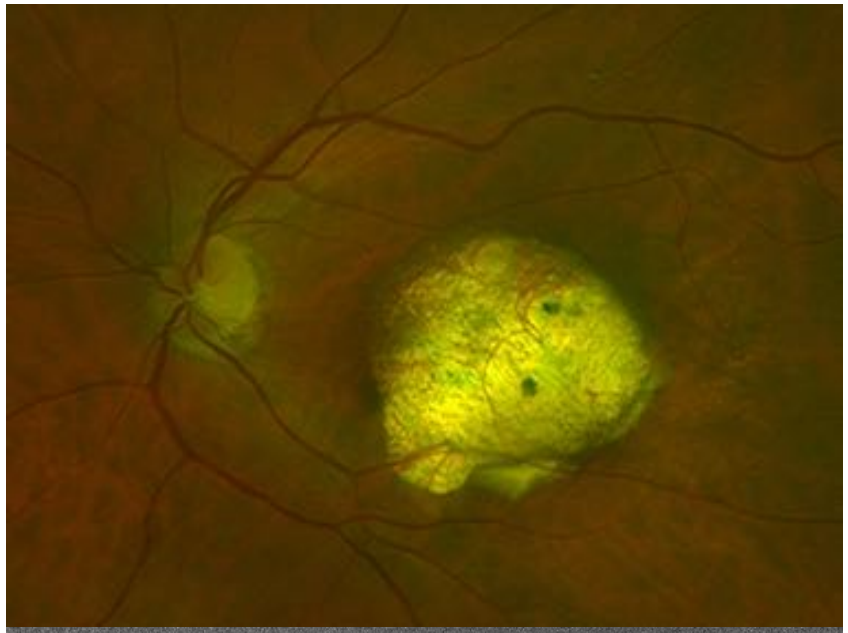


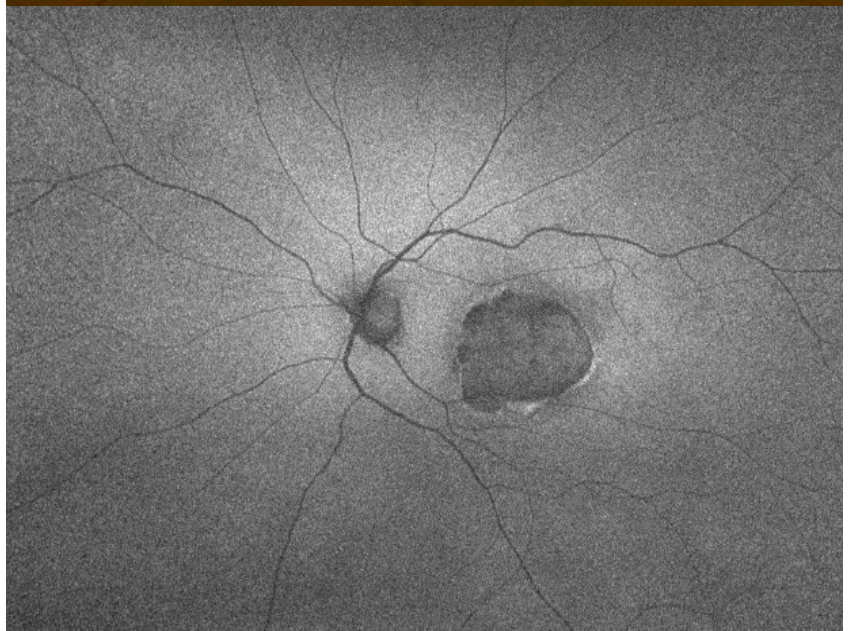


Patient 2 at 29 years old
NCMD grade 3
VA: 20/80 OS

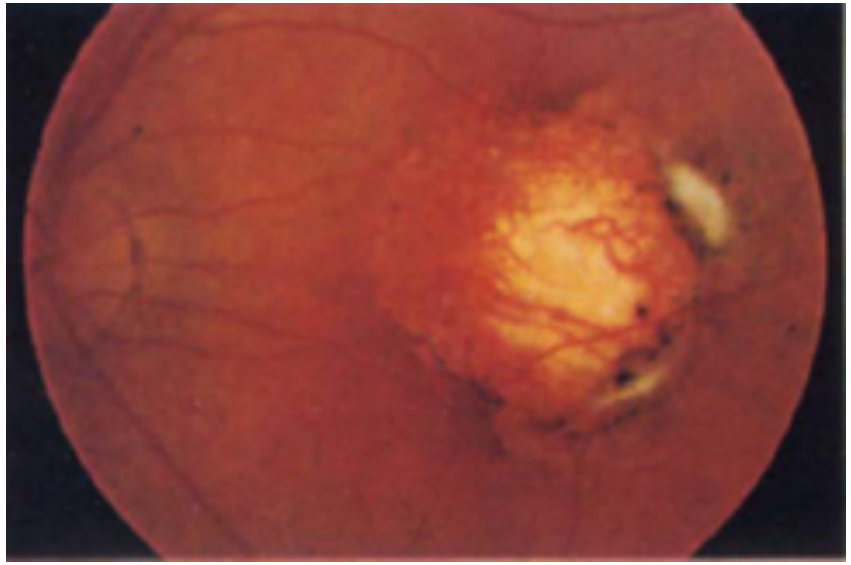


60 years old NCMD grade 3
20/100 OS

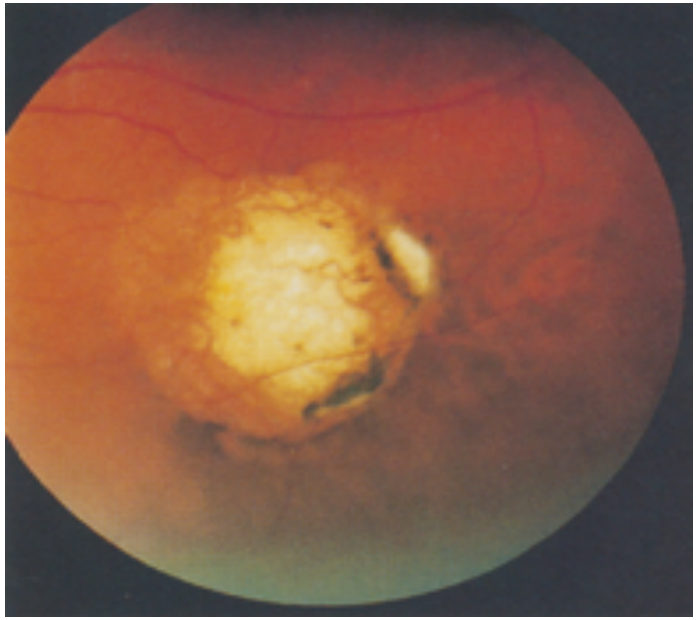




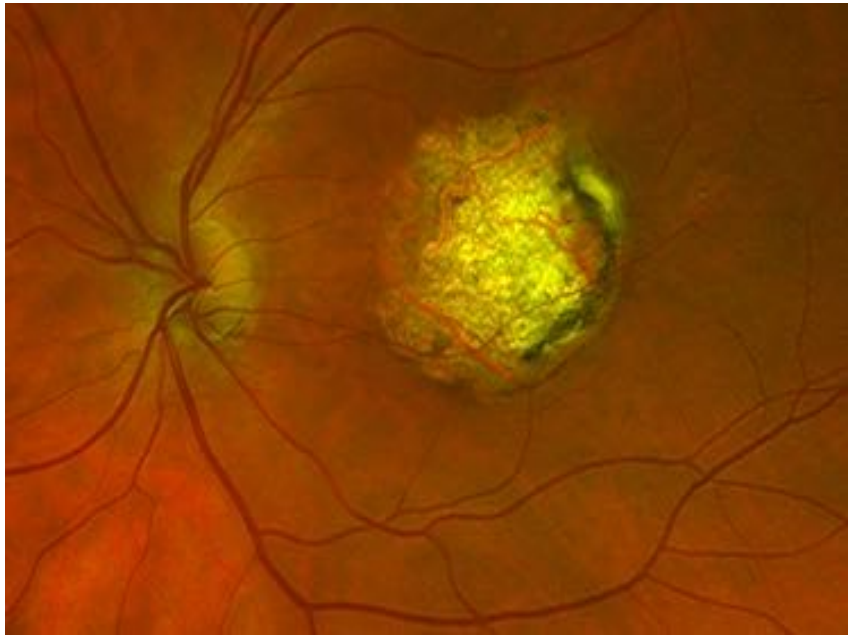
Patient 5 at 16 years old NCMD grade 3
VA: 20/40 OS



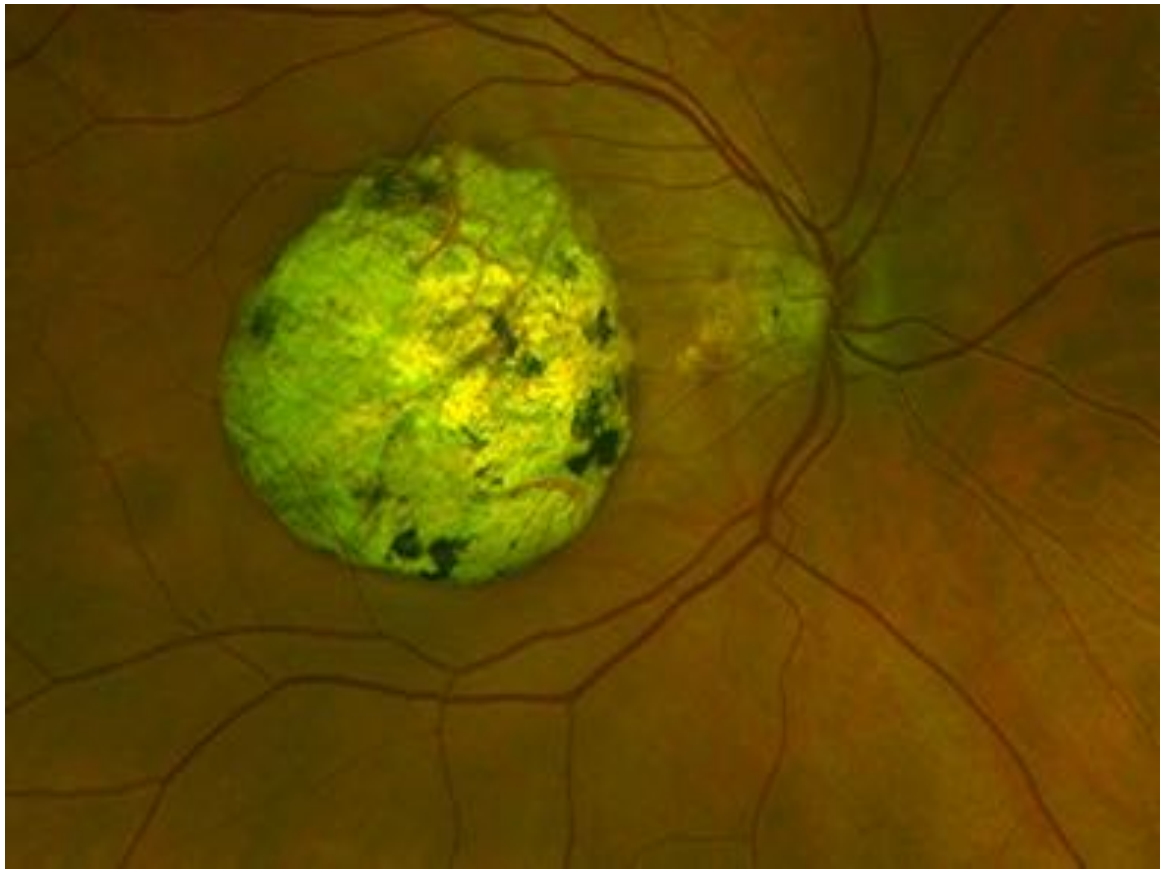
36 years old
NCMD grade 3
VA:20/40 OS

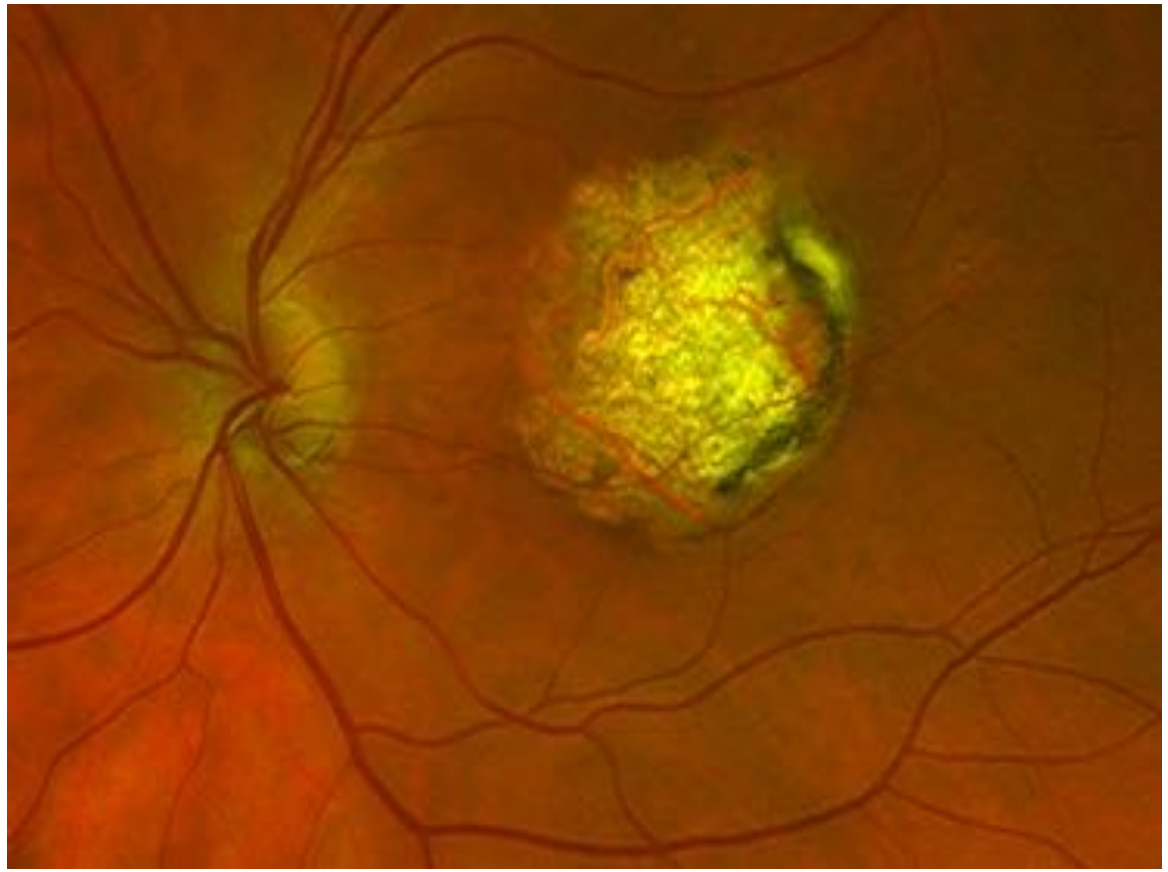


67 years old
NCMD grade 3
Va 20/60 OS

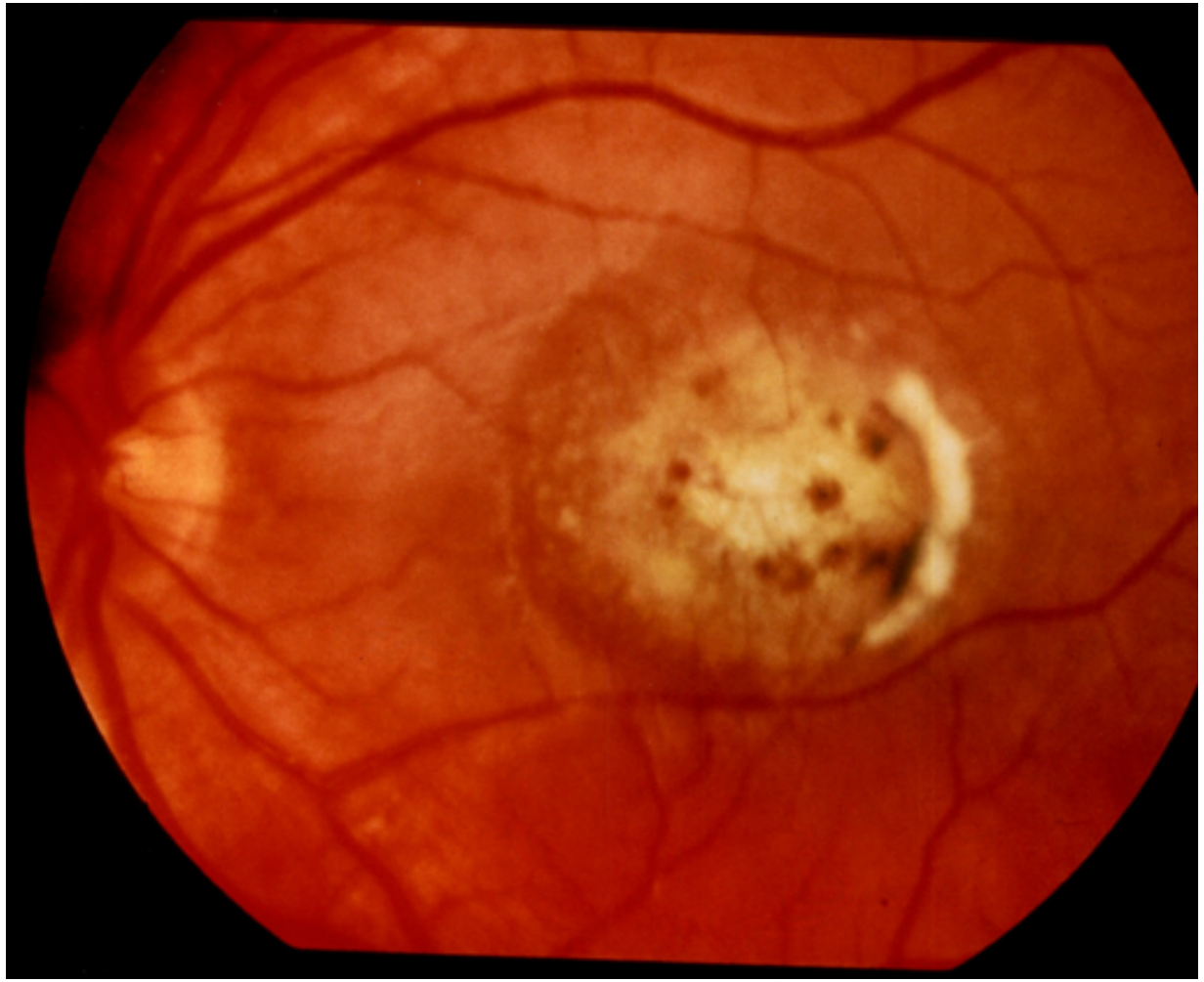


Patient 5 at 67 years old
NCMD grade 3
VA: 20/200 OD, 20/60 OS



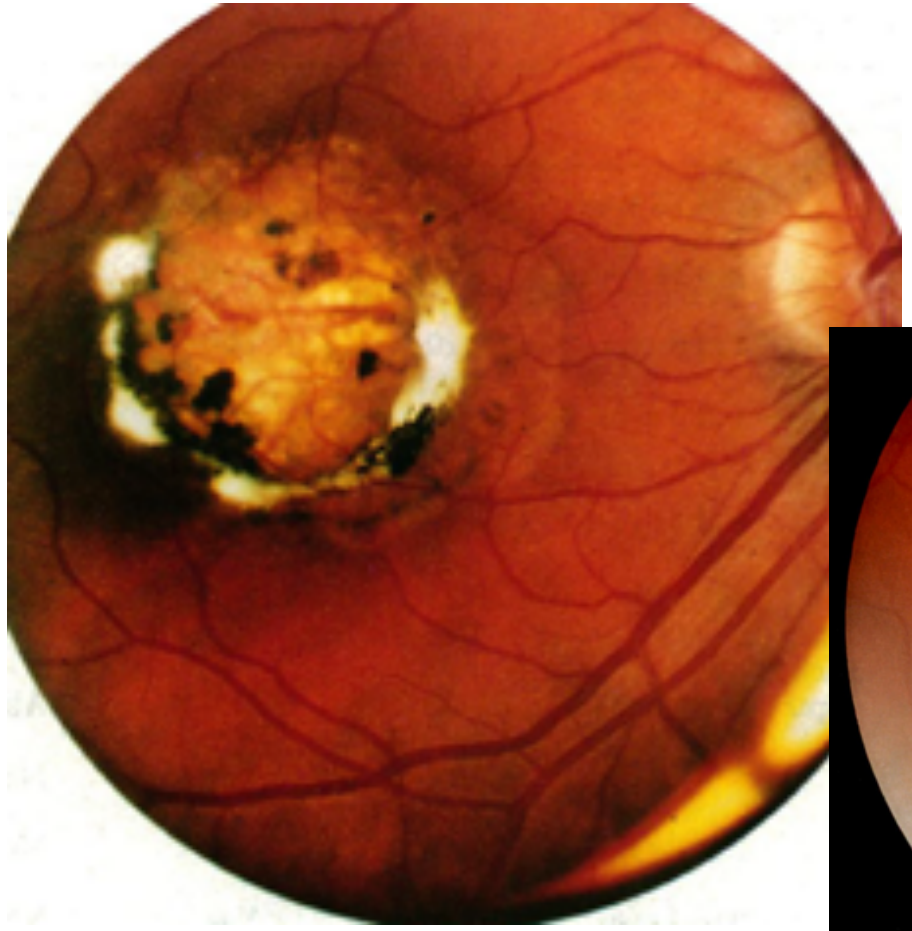


Patient 7 at 21 years old
NCMD grade 3
VA: 20/30 OD, 20/200 OS

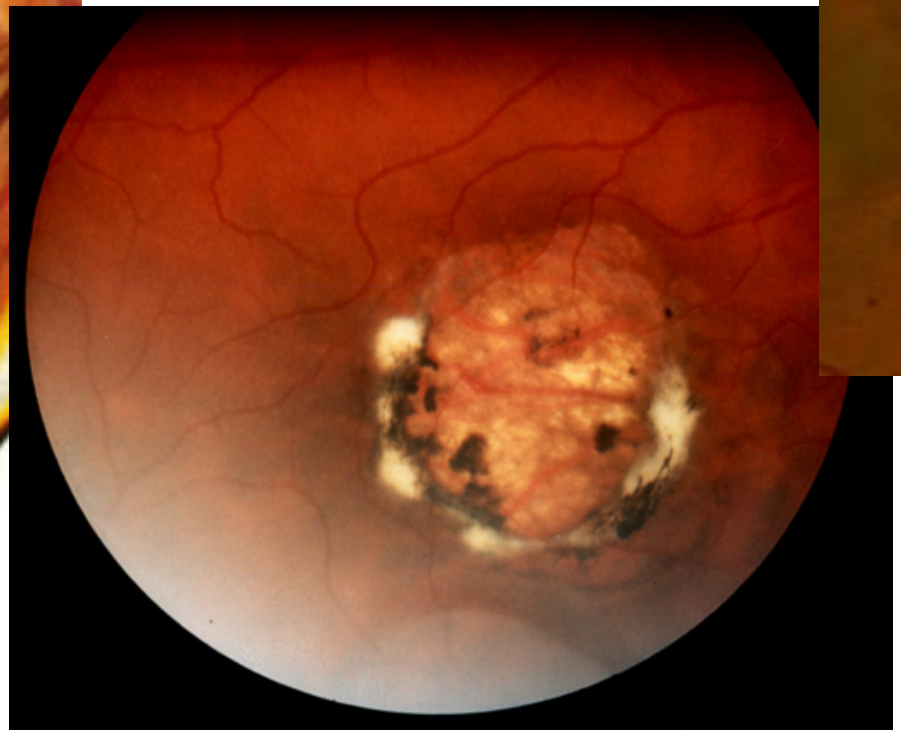


IMPROVED:
55 years old
NCMD grade 3
VA: 20/40 OD, 20/50 OS

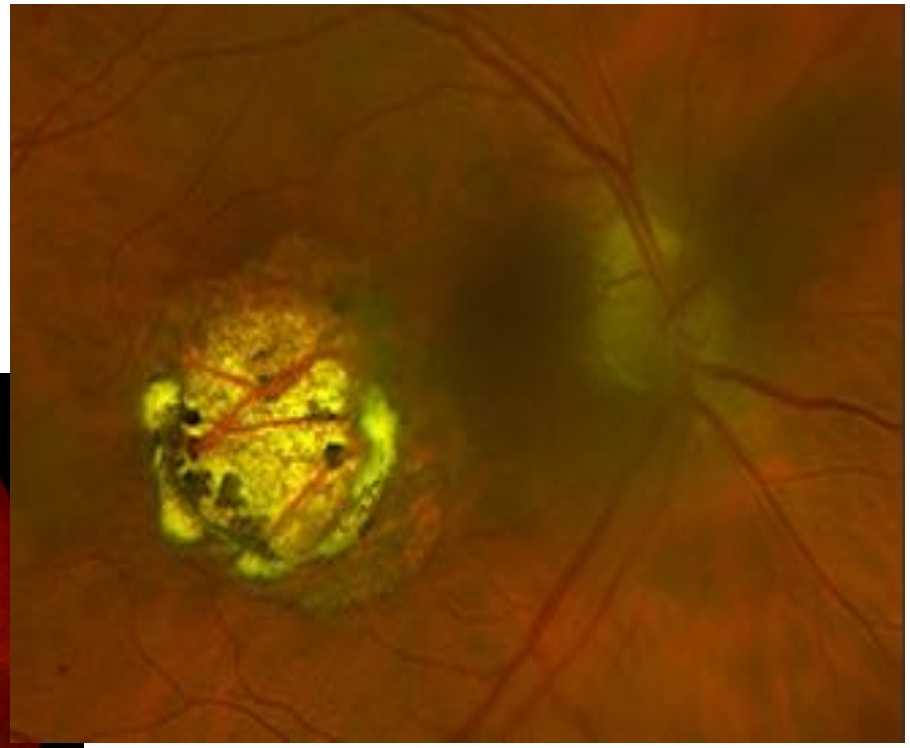
Patient 11 at 29 years old
NCMD grade 3
VA: 20/30 OU



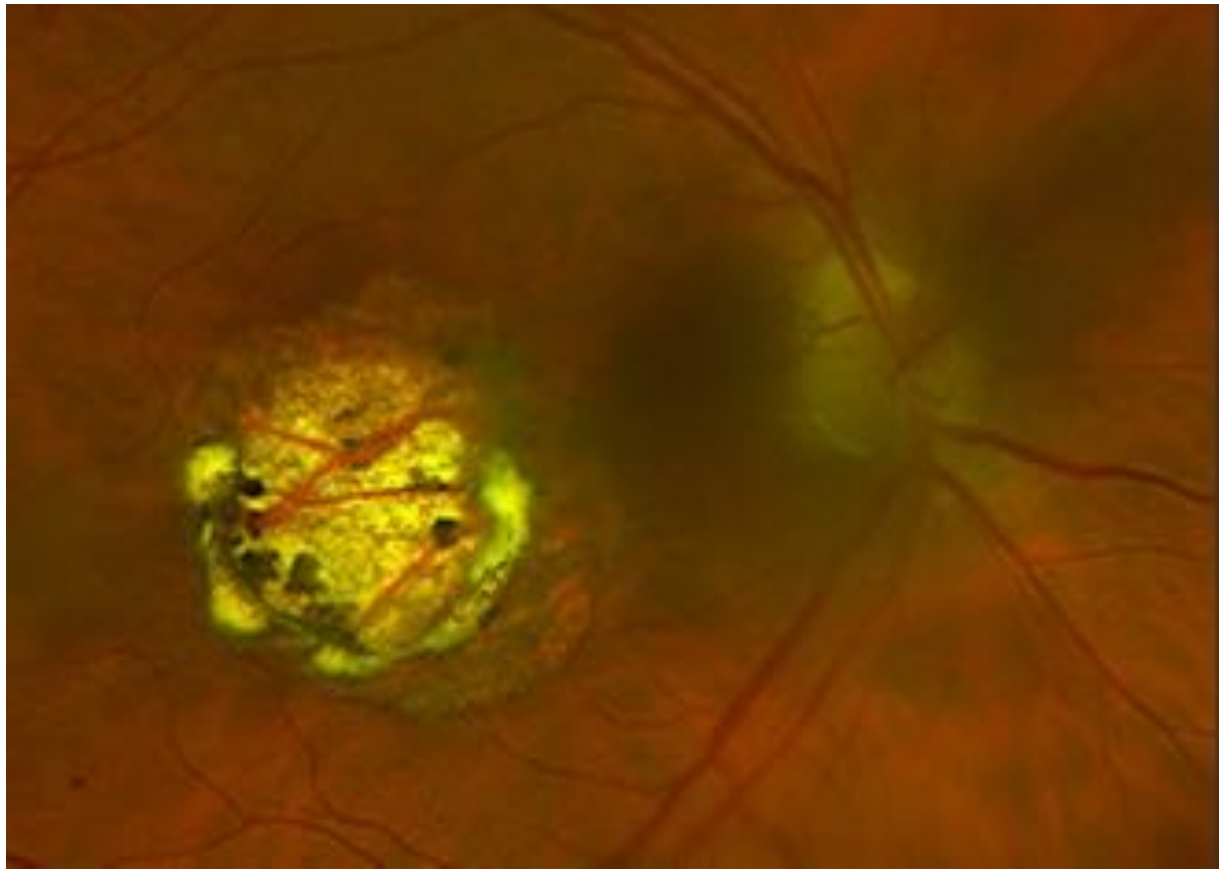
40 years old
NCMD grade 3
VA: 20/30 OU

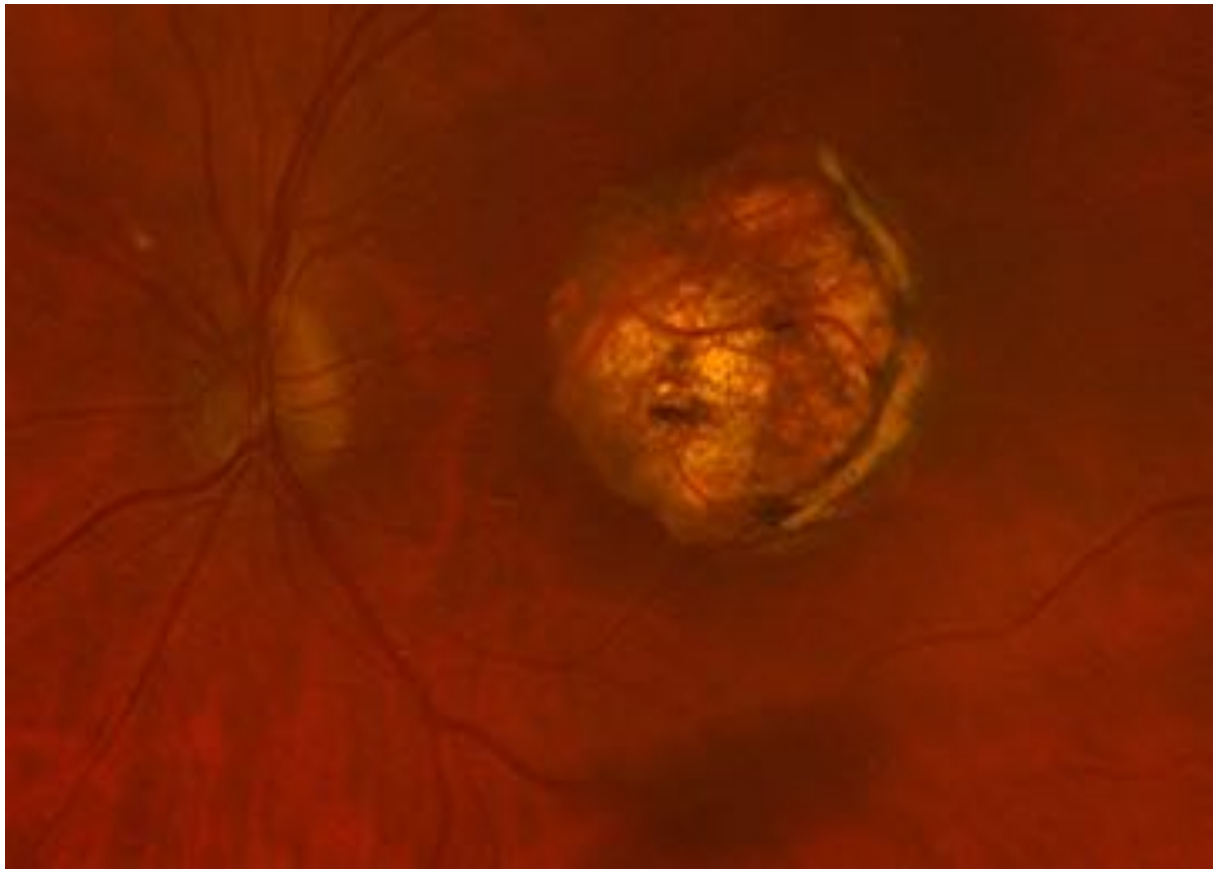


70 years old
NCMD grade 3
VA: 20/70 OU

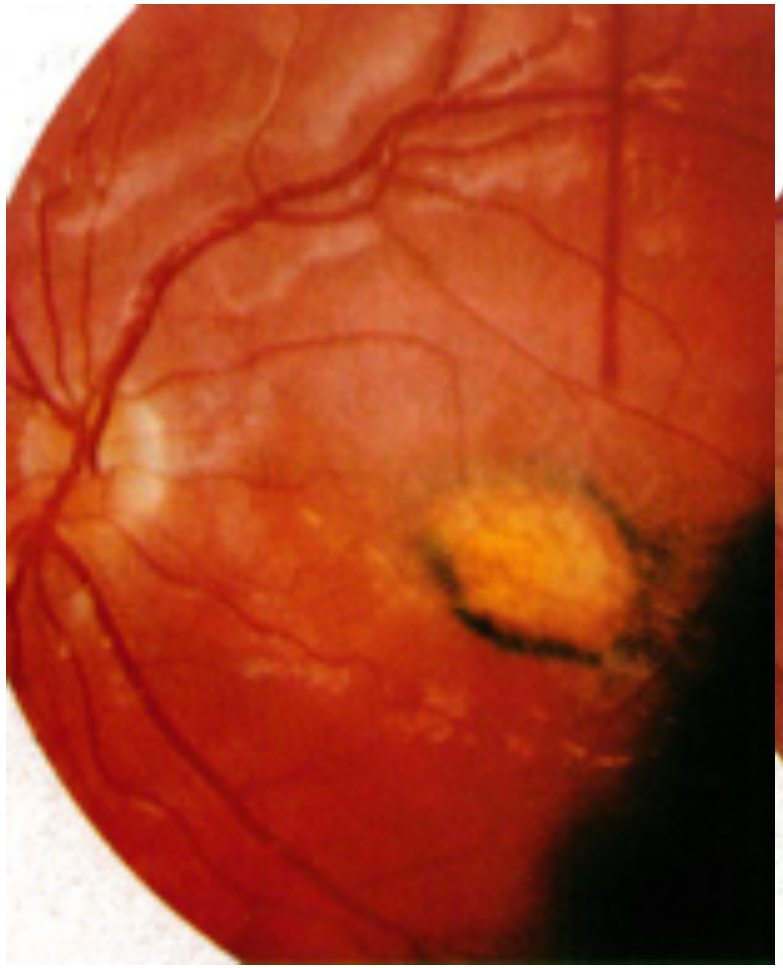


Patient 11 at 70 years old
NCMD grade 3
VA: 20/70 OU

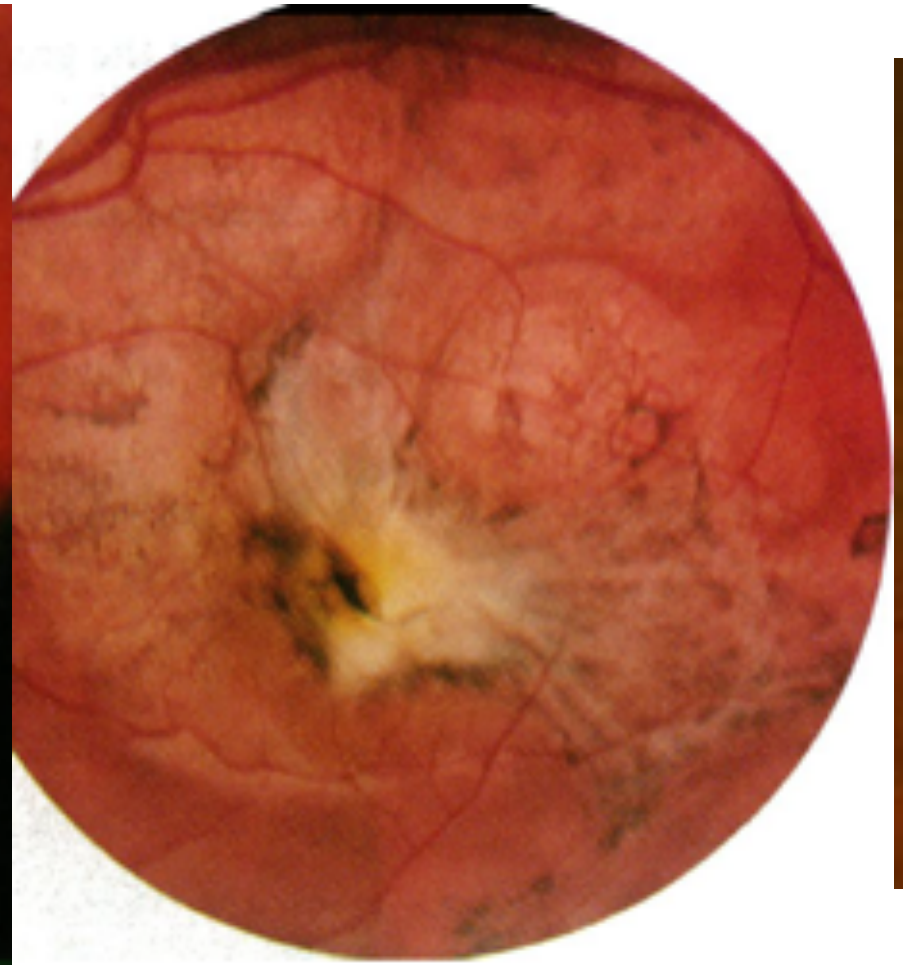




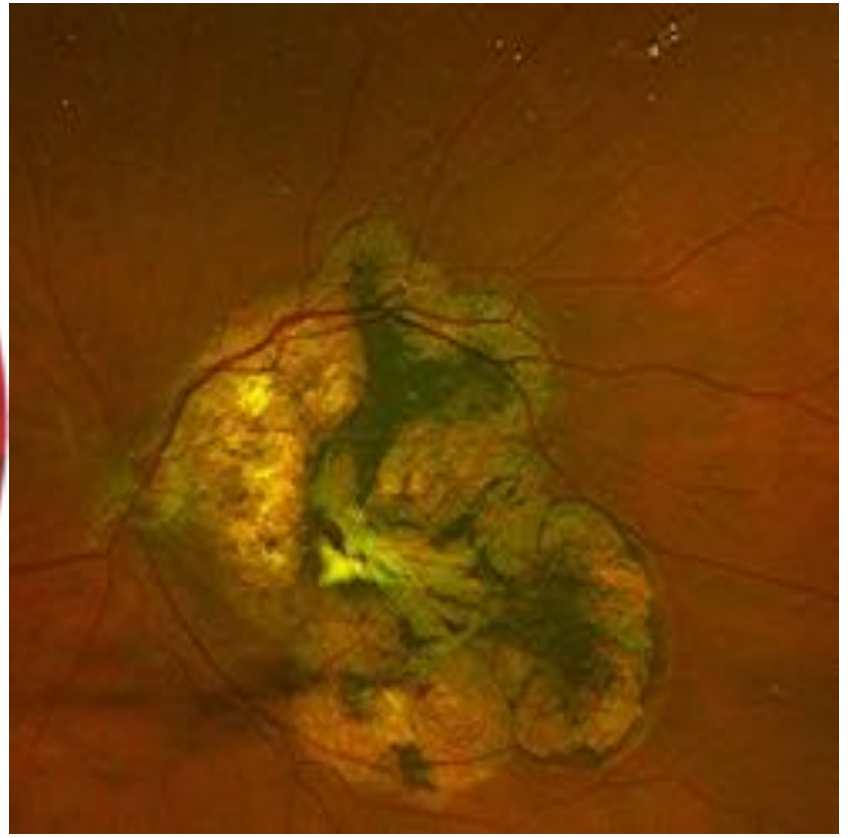
Patient 12 at 3 years old
NCMD Grade 2
VA: 20/30 OS



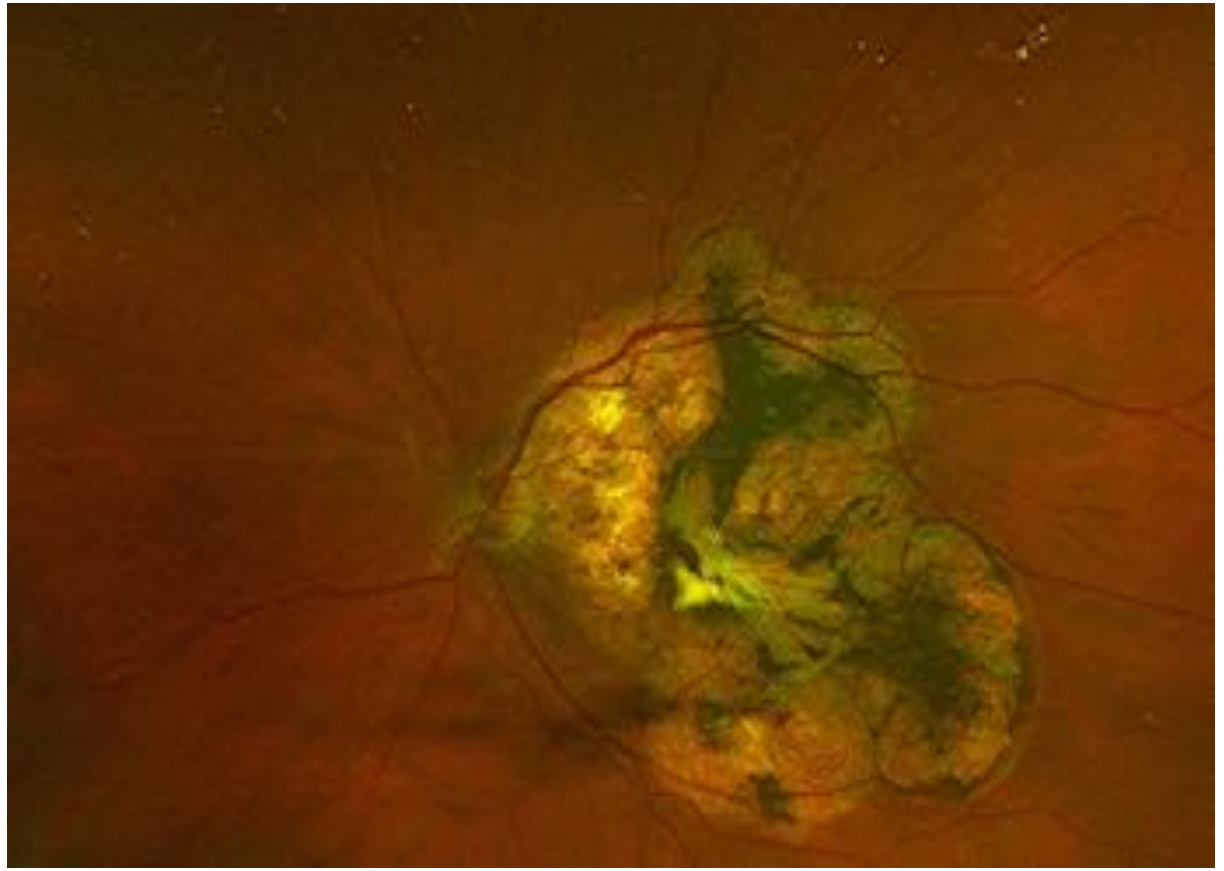
14 years old
NCMD grade 2
VA: 20/200 OS



51 years old
NCMD grade 2
VA: 20/250 OS



Patient 12 at 51 years old
NCMD grade 2
VA: 20/70 OD, 20/250 OS

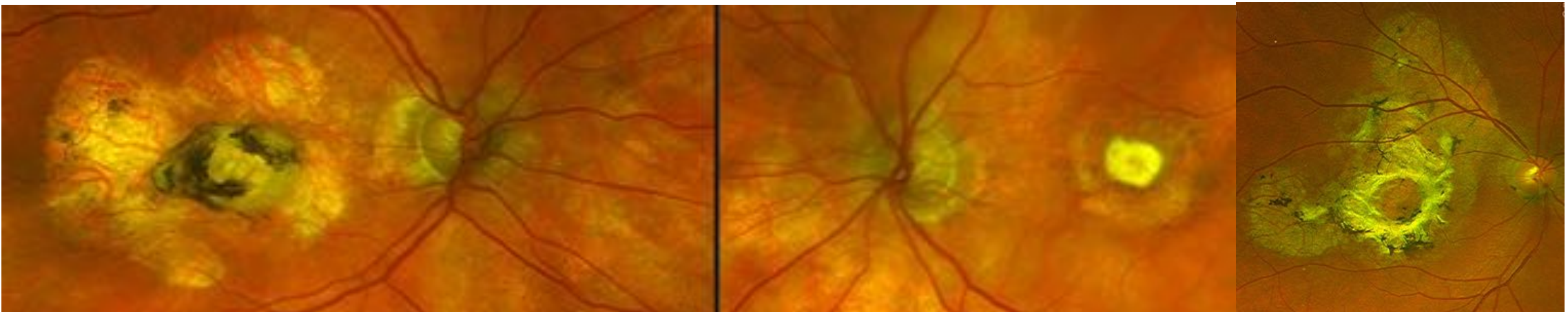


Visual Acuity Changes in the Original NCMD Family 765 (30-50 years later)

Name	Current Age	Previous VA OD	Previous VA OS	Current VA OD	Current VA OS	
1	80	20/30	20/50	20/50	20/80-1	STABLE
2	60	20/40	20/80	20/40-2	20/100-1	STABLE
3	15	NA	NA	20/20+1	20/15-1	STABLE
4	56	20/40	6/200	20/20	20/200	STABLE
5	67	20/100	20/40	20/200	20/60-2	STABLE
6	37	20/25+2	20/30	20/40-2	20/150-2	OS WORSE
7	55	20/30	20/200	20/40	20/50	OS IMPROVED
8	18	NA	NA	20/80-1	20/60-1	
9	39	NA	NA	20/20	20/20	
10	13	NA	NA	20/40-2	20/30+2	
11	70	20/30	20/30	20/70-2	20/70	STABLE
12	51	HM	20/50	20/70	20/250	OD IMPROVED OS WORSE
13	25	NA	NA	20/30	20/20-2	
14	45	2060+2	20/70-1	20/150-1	20/250	STABLE
15	49	20/30	20/70	20/100-2	20/150	WORSE OU
16	16	NA	NA	20/20-2	20/20-2	
17	81	20/20-3	20/20-3	20/20-2	20/25	STABLE
18	83	20/40	20/30	CF @ FACE	20/40	OD WORSE
19	45	20/25	20/40	HM	20/40	OD WORSE
20	23	NA	NA	20/30-1	20/30-1	STABLE
21	40	20/20	20/25	20/15-2	20/40-2	STABLE
22	15	NA	NA	20/40	20/30-2	
23	64	20/200	20/40	20/100-2	20/50-1	STABLE
24	11	NA	NA	20/25+1	20/15-1	

Conclusion

- Most NCMD patients have stable vision and fundus findings throughout their lives even up to 50 years follow-up.
- The ones who lost vision did so with NCMD grade 2, rarely grade 3
    - developed choroidal neovascularization
    - More common than previously recognized
- anti-VEGFs may benefit these patients



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