Curing Usher Syndrome

Edwin M. Stone, M.D., Ph.D.

Financial Disclosures

NONE


WILLIAM J. KIMBERLING
USHER RESEARCH
LABORATORY
The William J. Kimberling Usher Research Laboratory
William
Kimberling

Realistic

HOPE

Realistic

HOPE

1) Plans that will work
2) A committed team

Three Questions

- When?
- But, what if . . .?
- How close are we?

When?

When?

As soon as humanly possible.

But, what if . . .?

But, what if . . .?

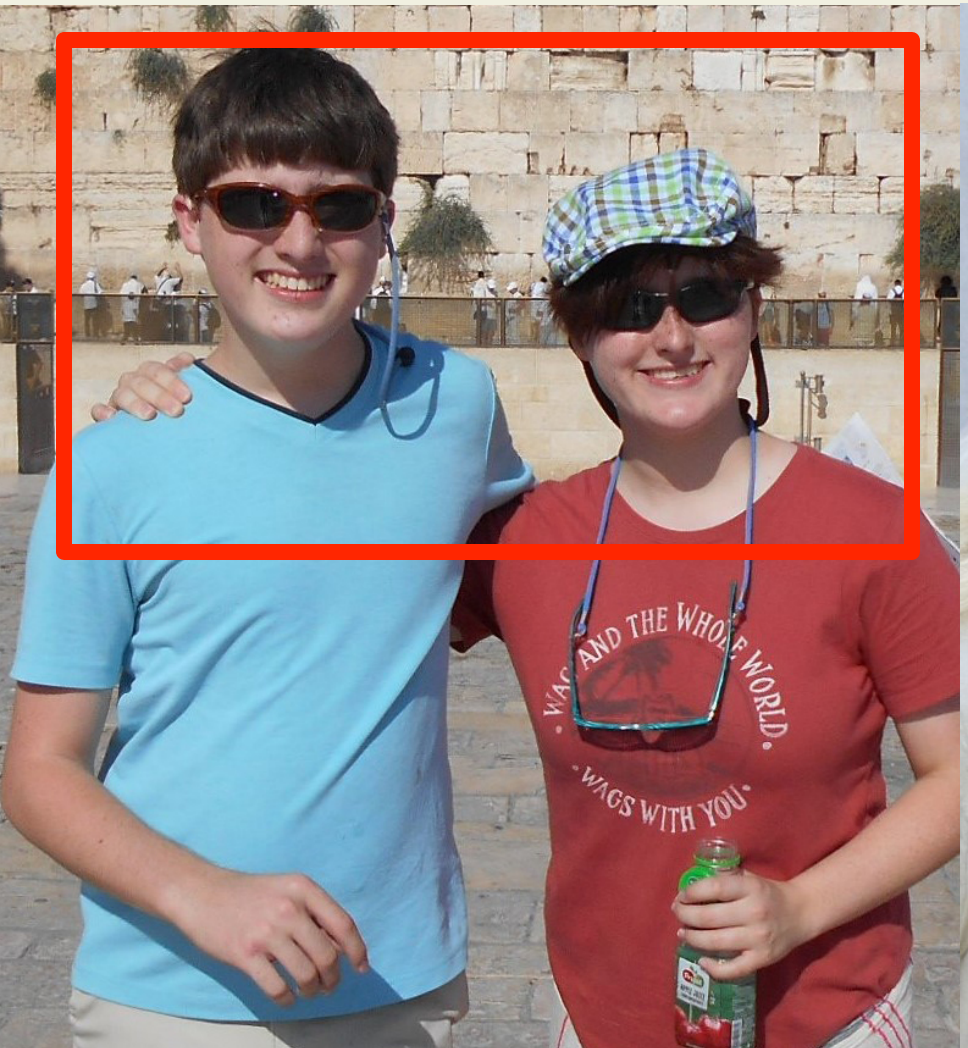
We will fix it.

How close are we?


Close enough to walk!
assets.dnainfo.com

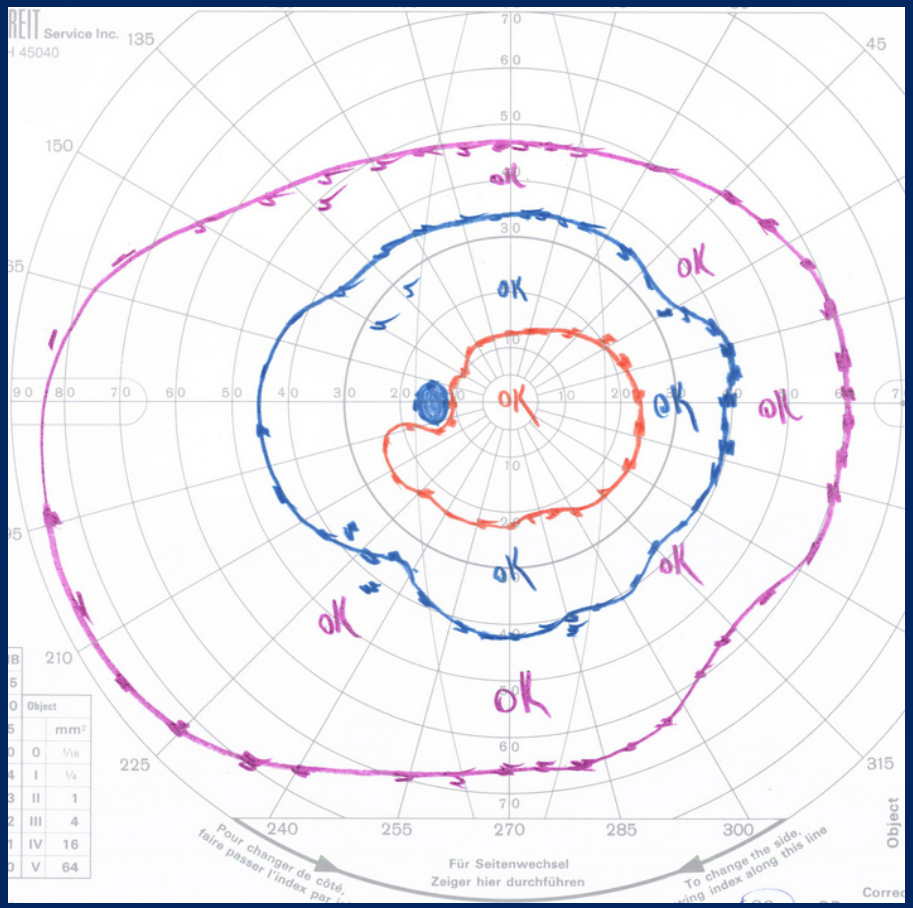
What will success look like?

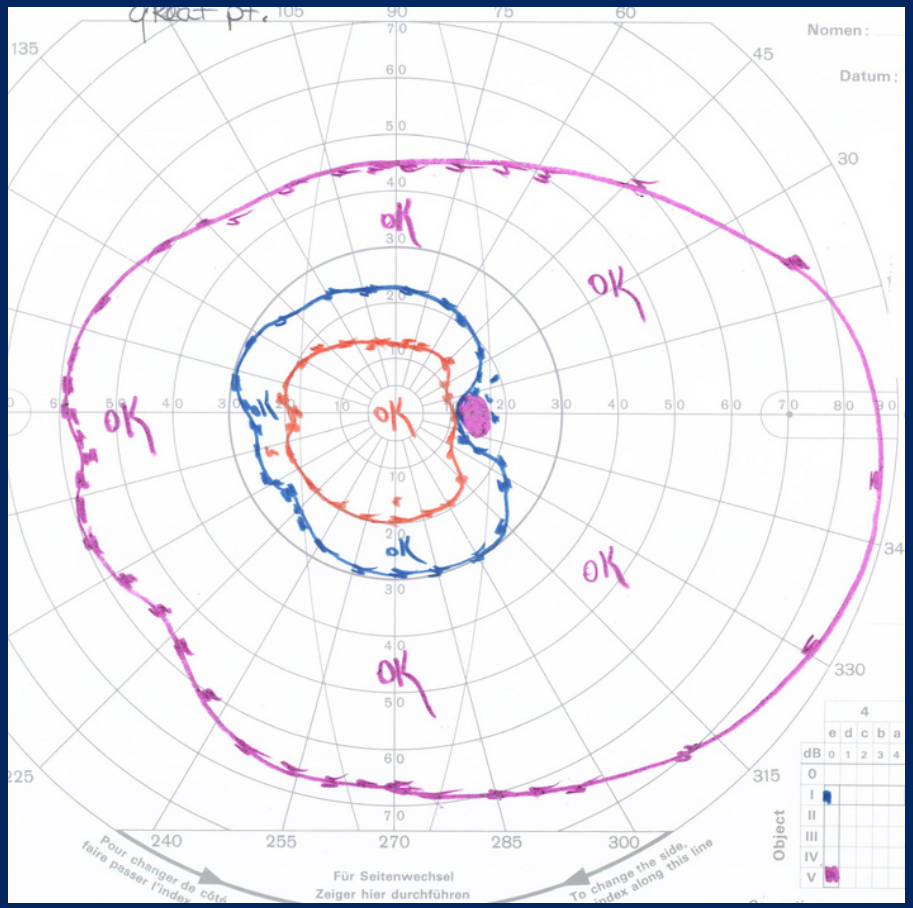
What will success look like?

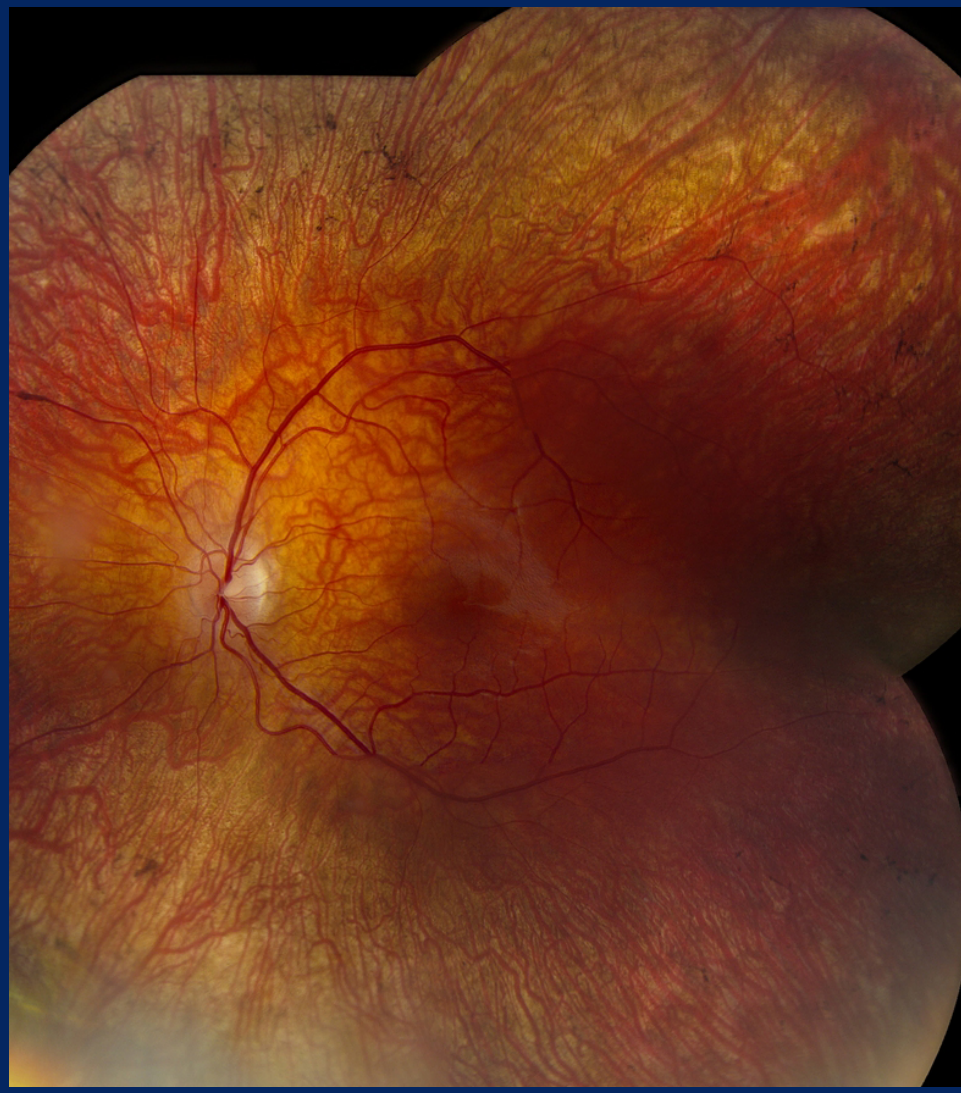


Case Report

- 14 year old twins
- Hearing loss noticed as newborns
- Bilateral cochlear implants
- 20/25
- Some difficulty in dim light


Service Inc.
H 45040
135
45
150
30
210
330
225
315
240
255
270
285
300
ok
Object
mm²
0 1/16
I 1/4
II 1
III 4
IV 16
V 64
Für Seitenwechsel
Zeiger hier durchführen
To change the side,
Pour changer de côté,


Nomen:
Datum:
135
45
150
30
210
330
225
315
240
255
270
285
300
ok
Object
dB 0 1 2 3 4
I
II
III
IV
V
Für Seitenwechsel
Zeiger hier durchführen
To change the side,
Pour changer de côté,



Case Report

- Clinical diagnosis: Type I Usher Syndrome

Case Report

- Clinical diagnosis: Type I Usher Syndrome
- Molecular Test: $575

Case Report

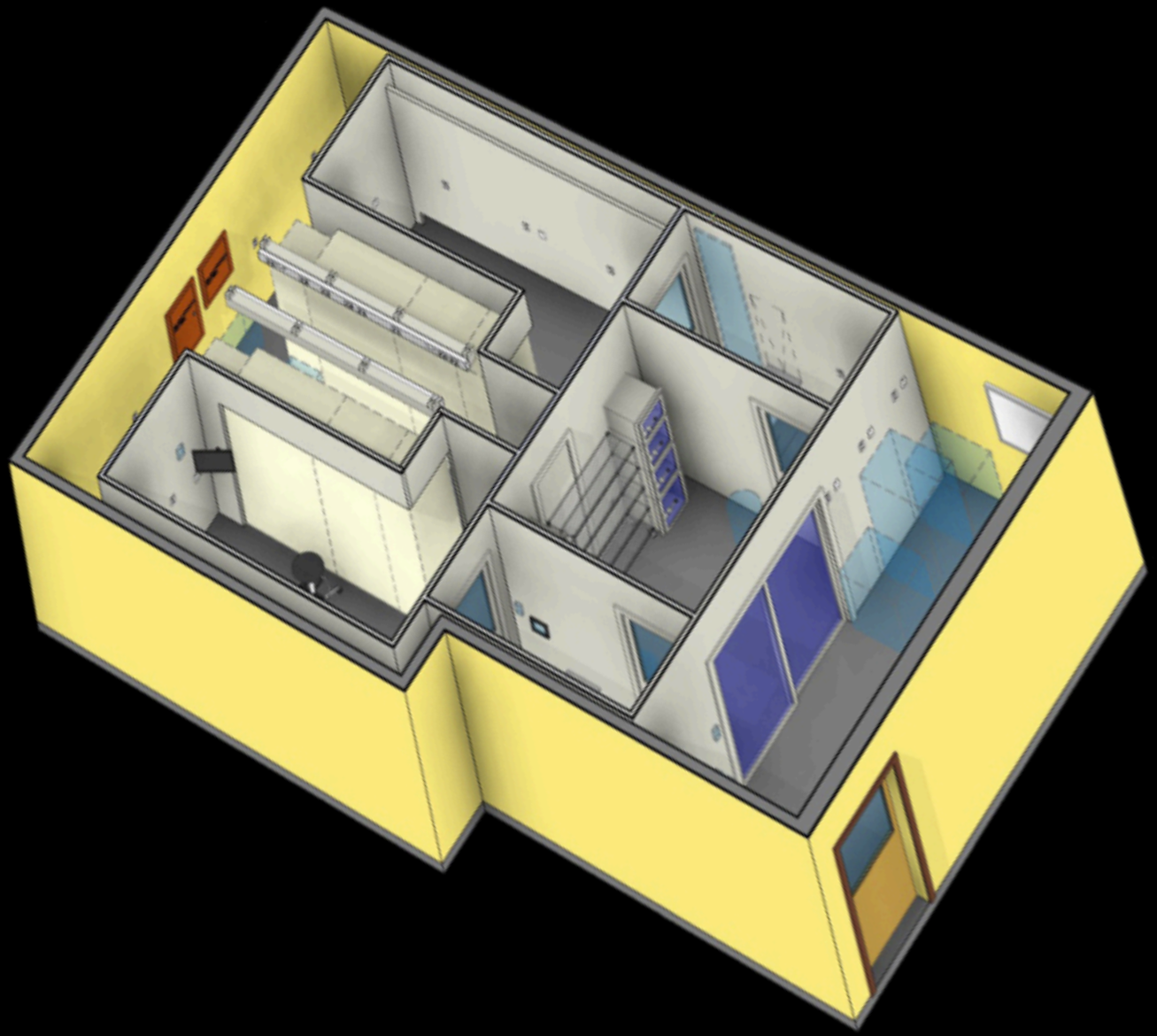
- Clinical diagnosis: Type I Usher Syndrome
- Molecular Test: $575
- Result: *USH1C*

  Val72Val (splice variant), Thr78insC

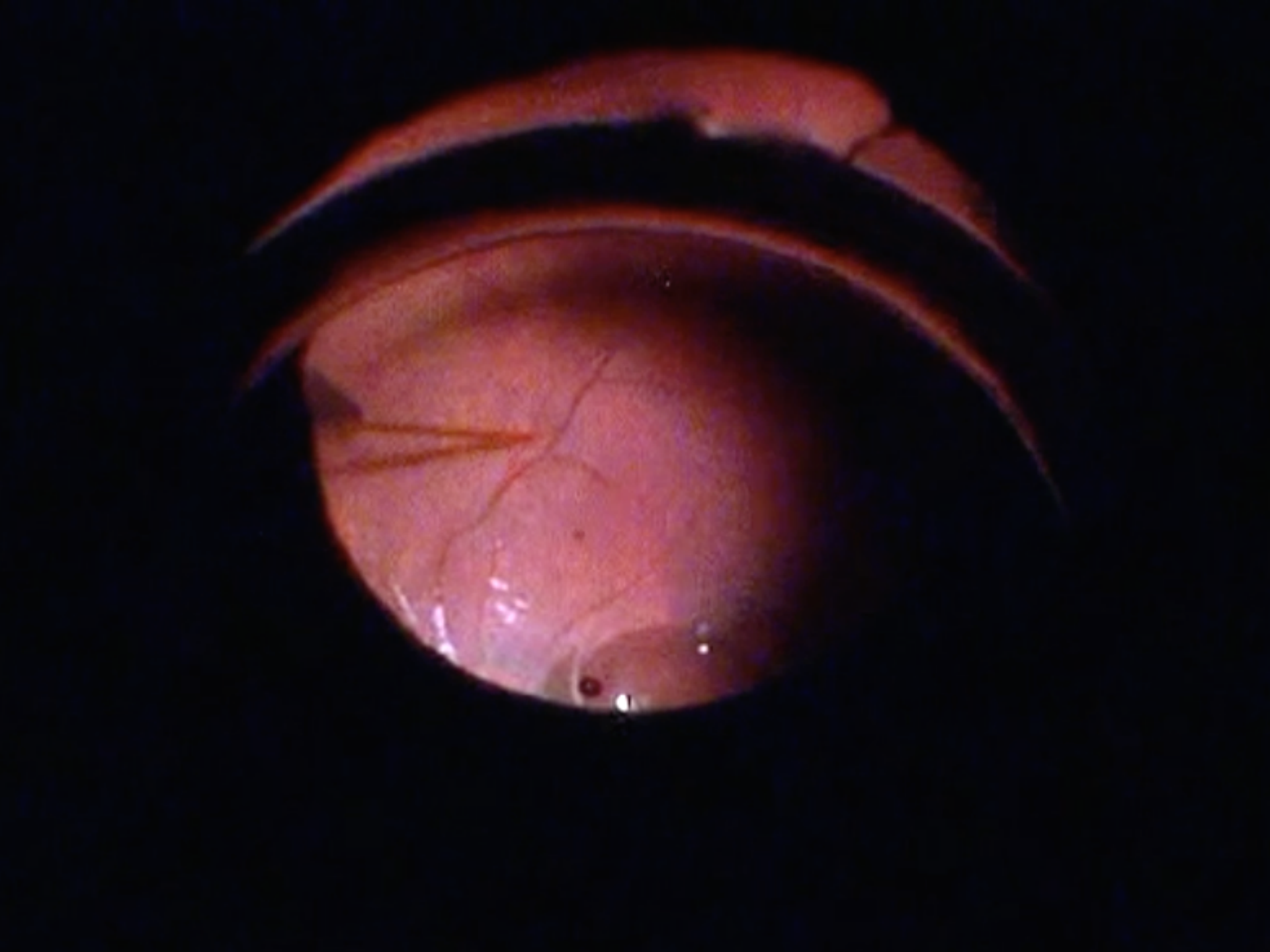
Project Usher

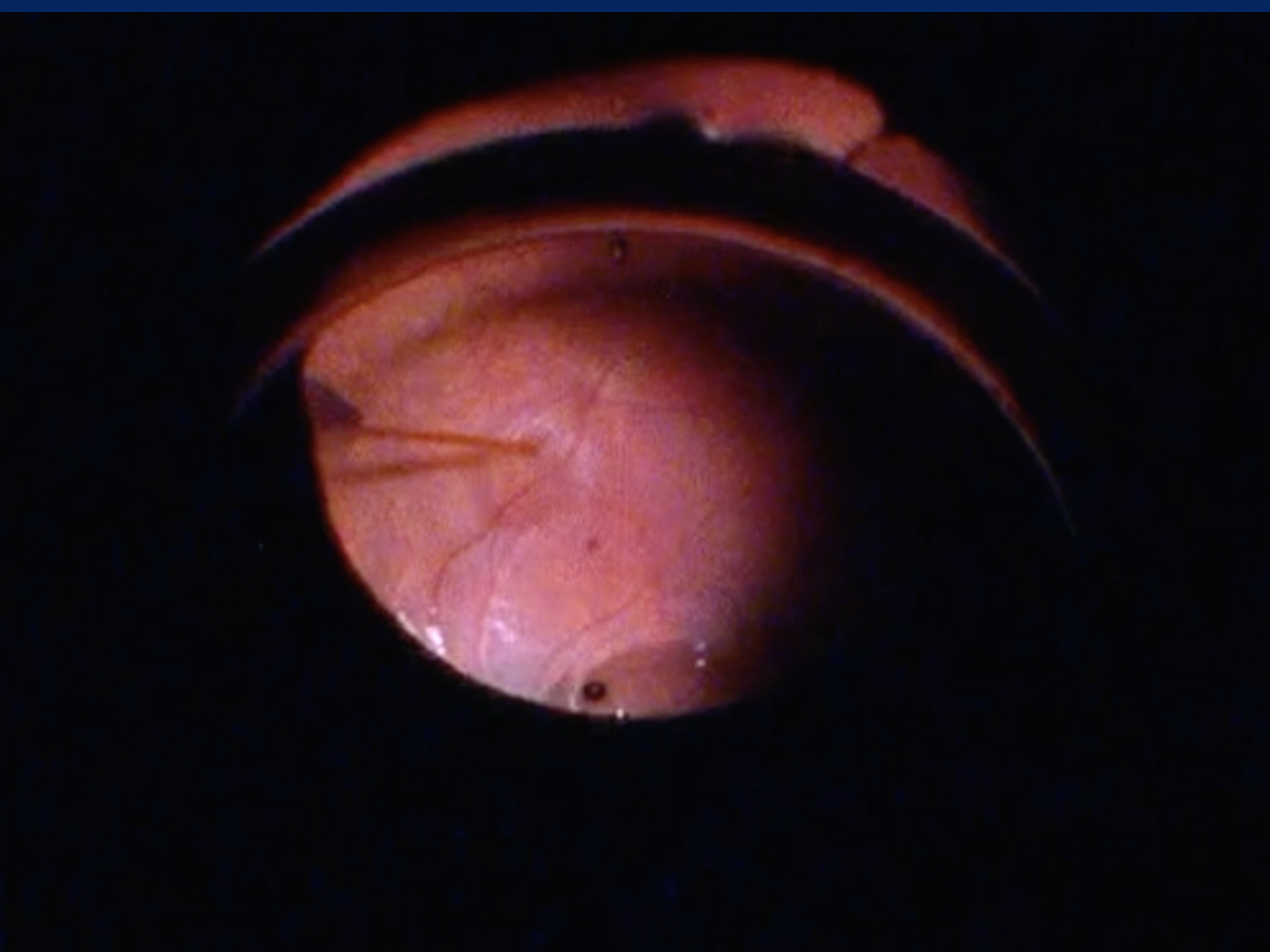
www.projectusher.org

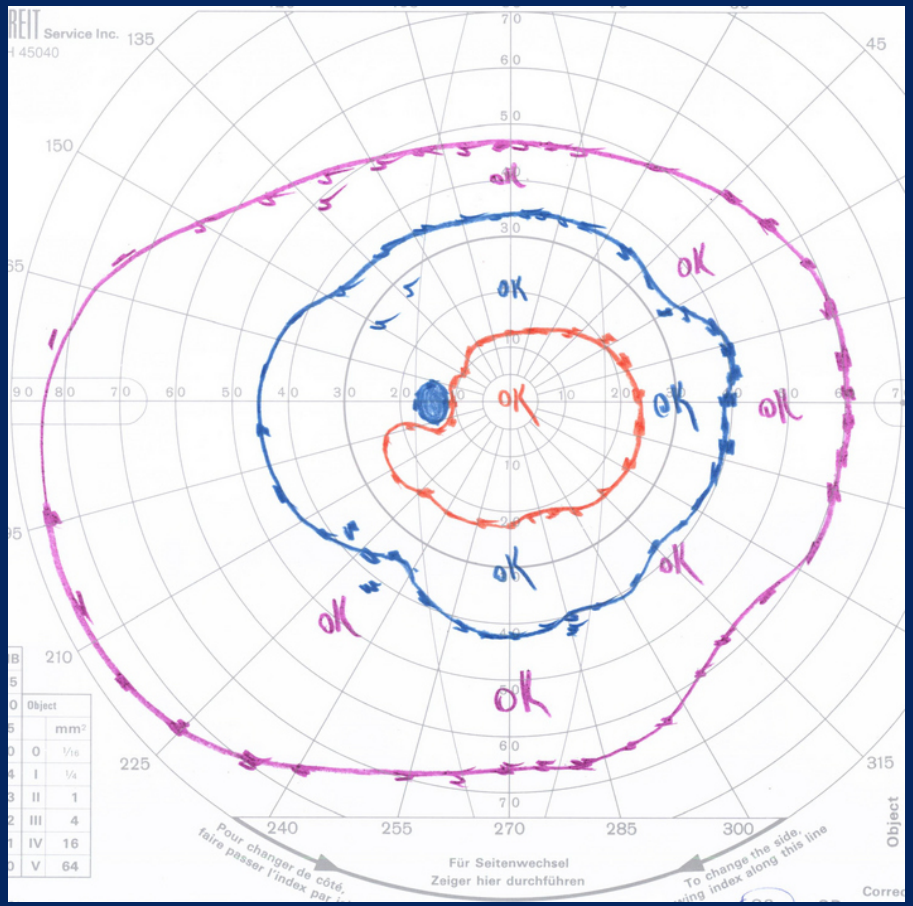
Steven W. Dezii Research Facility

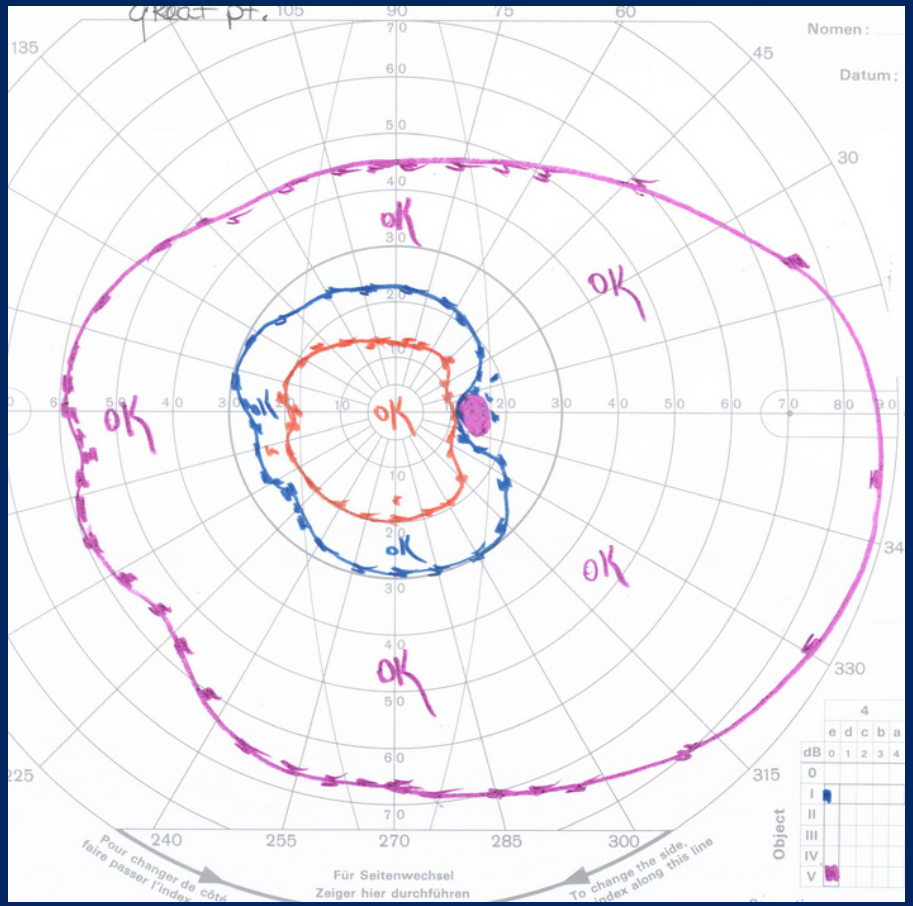


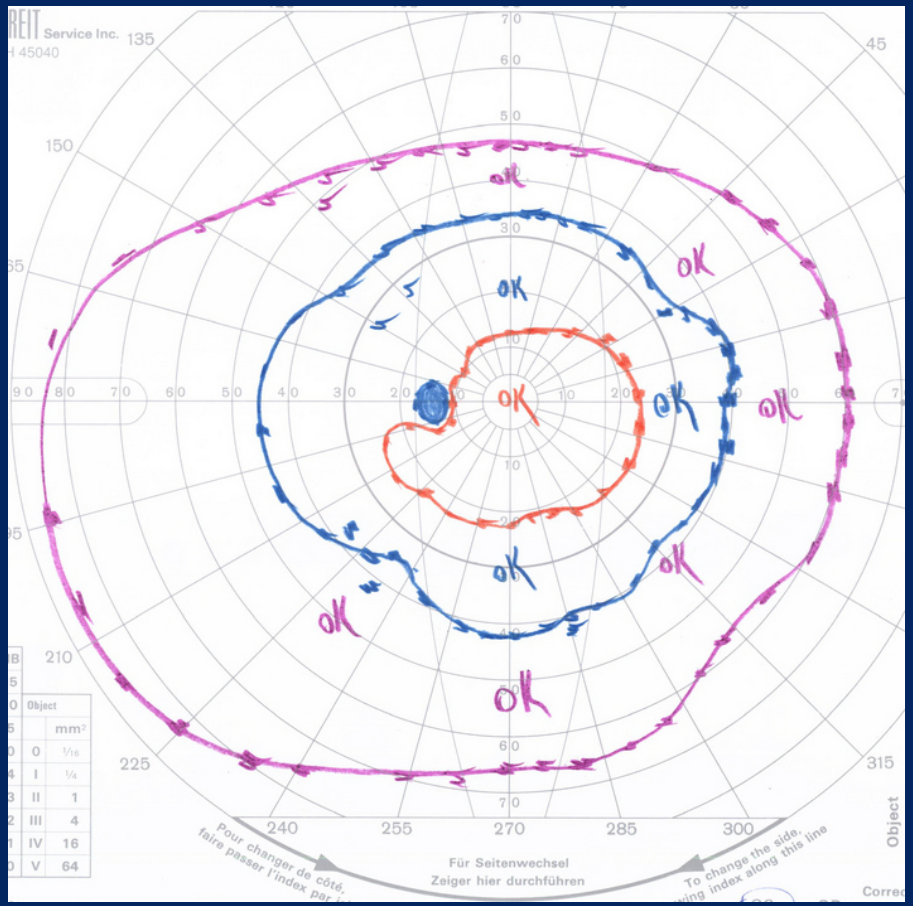

Nurse

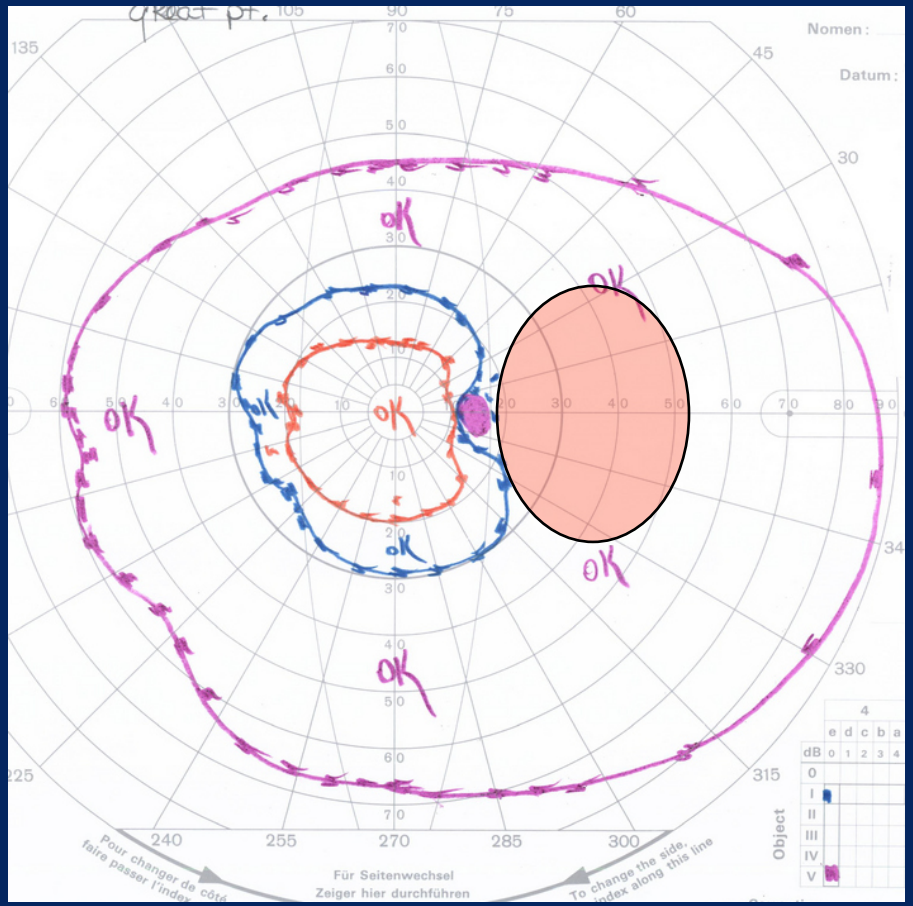


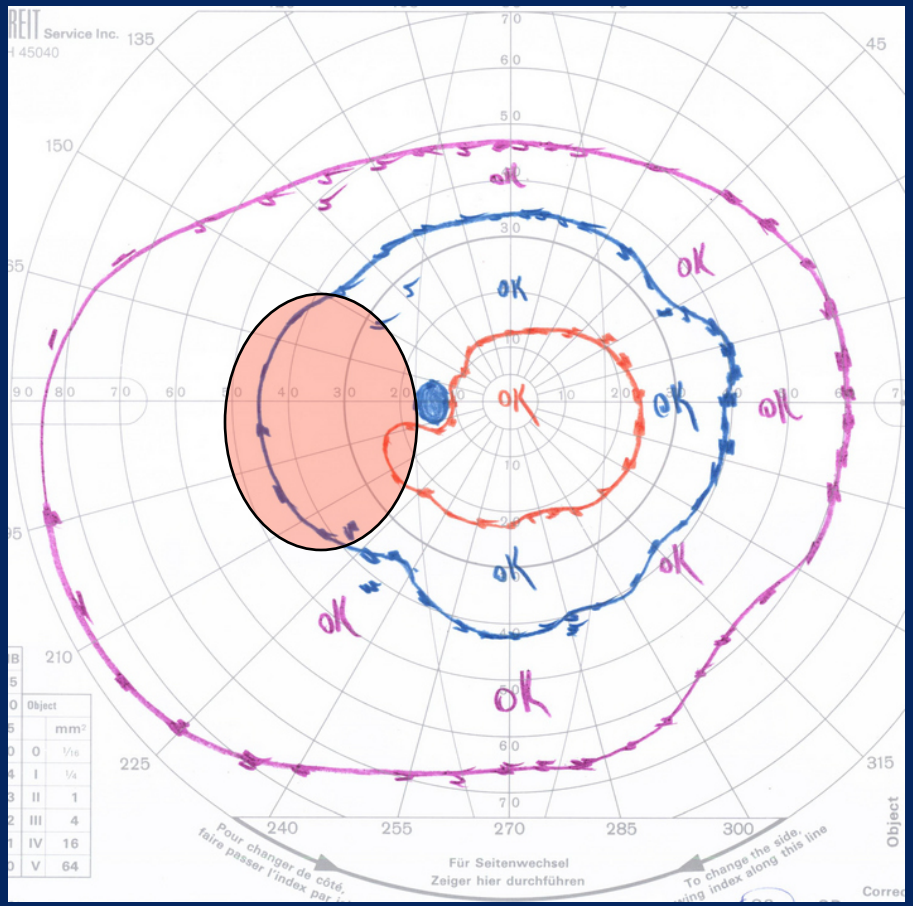


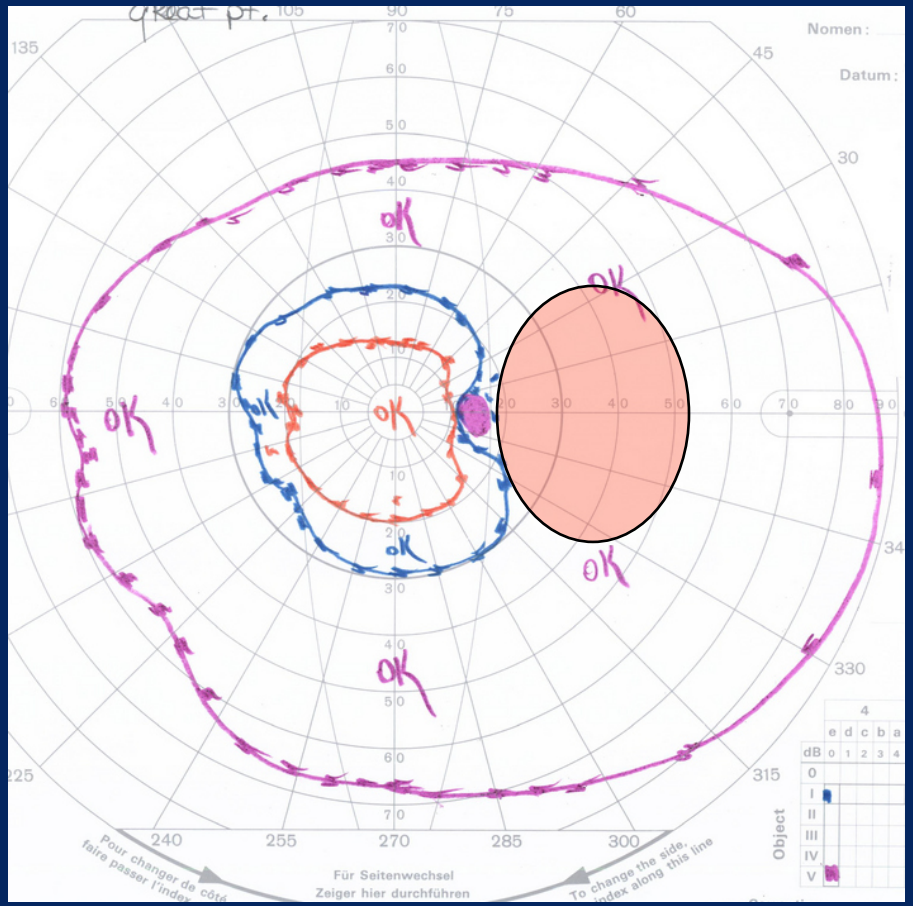

Service Inc.
H 45040
OK
Object
mm²
0 1/16
I 1/4
II 1
III 4
IV 16
V 64
Für Seitenwechsel
Zeiger hier durchführen
Pour changer de côté,
To change the side,
Object


Nomen:
Datum:
OK
dB
Object
Für Seitenwechsel
Zeiger hier durchführen
Pour changer de côté,
To change the side,


Service Inc.
H 45040
135
45
150
210
225
240
255
270
285
300
315
Object
mm²
0
I
II
III
IV
V
Für Seitenwechsel
Zeiger hier durchführen
Pour changer de côté,
To change the side,


Nomen:
Datum:
135
45
30
330
315
225
240
255
270
285
300
Object
dB
Für Seitenwechsel
Zeiger hier durchführen
Pour changer de côté,
To change the side,


Service Inc.
H 45040
OK
Object
mm²
Für Seitenwechsel
Zeiger hier durchführen
To change the side,
Pour changer de côté,


Nomen:
Datum:
OK
Object
Für Seitenwechsel
Zeiger hier durchführen
To change the side,
Pour changer de côté,

Cost?

Less than $20,000 (including ten years of follow up).

What will success look like?

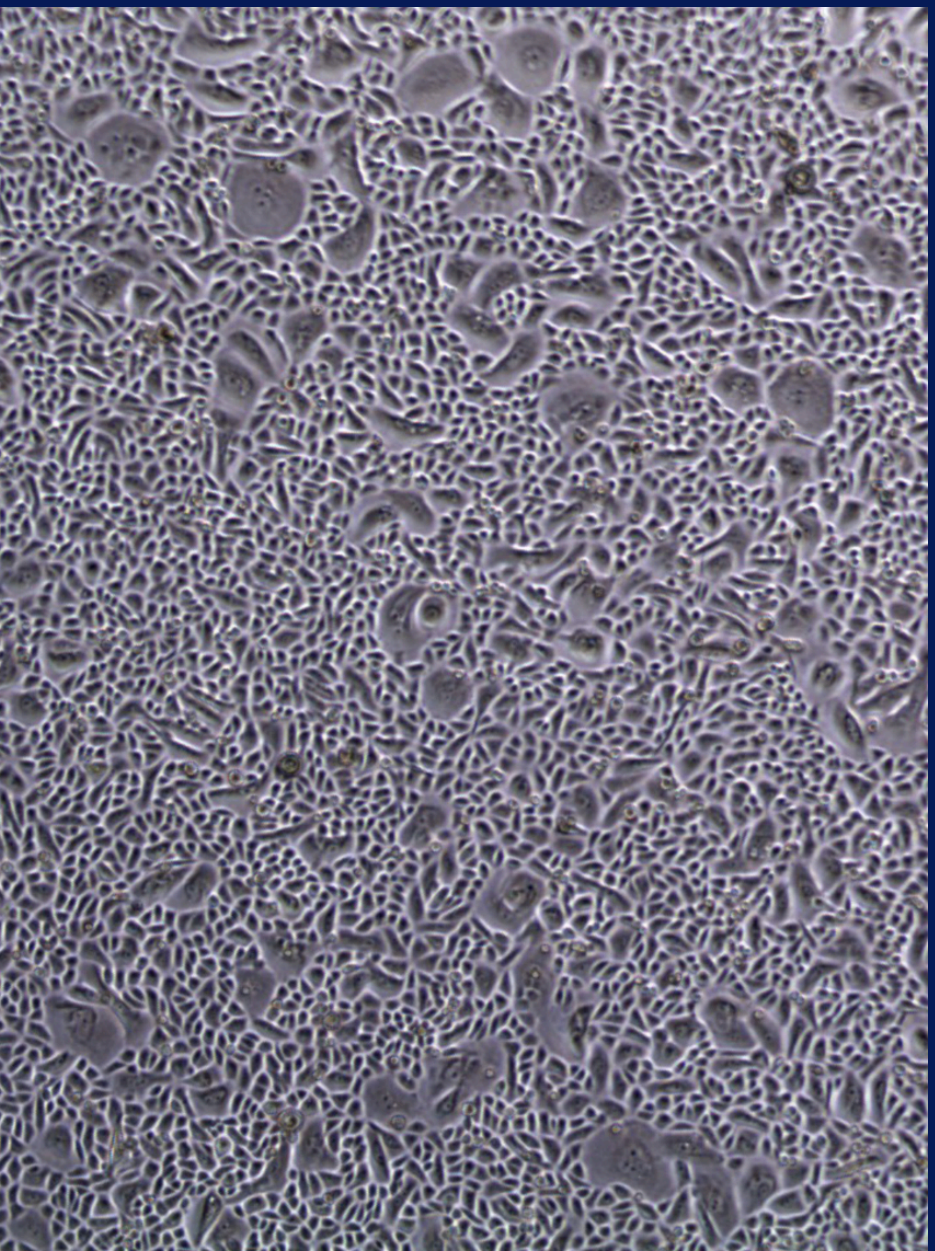
Case Report

- 59 year old woman
- Hearing loss noticed in early childhood (hearing aids)
- RP discovered at age 15
- Now sees only “hand motions” in both eyes

We need to:

- Skin -> stem cells -> retinal cells
- Dissolvable polymer support
- Transplanted into the subretinal space of the macula

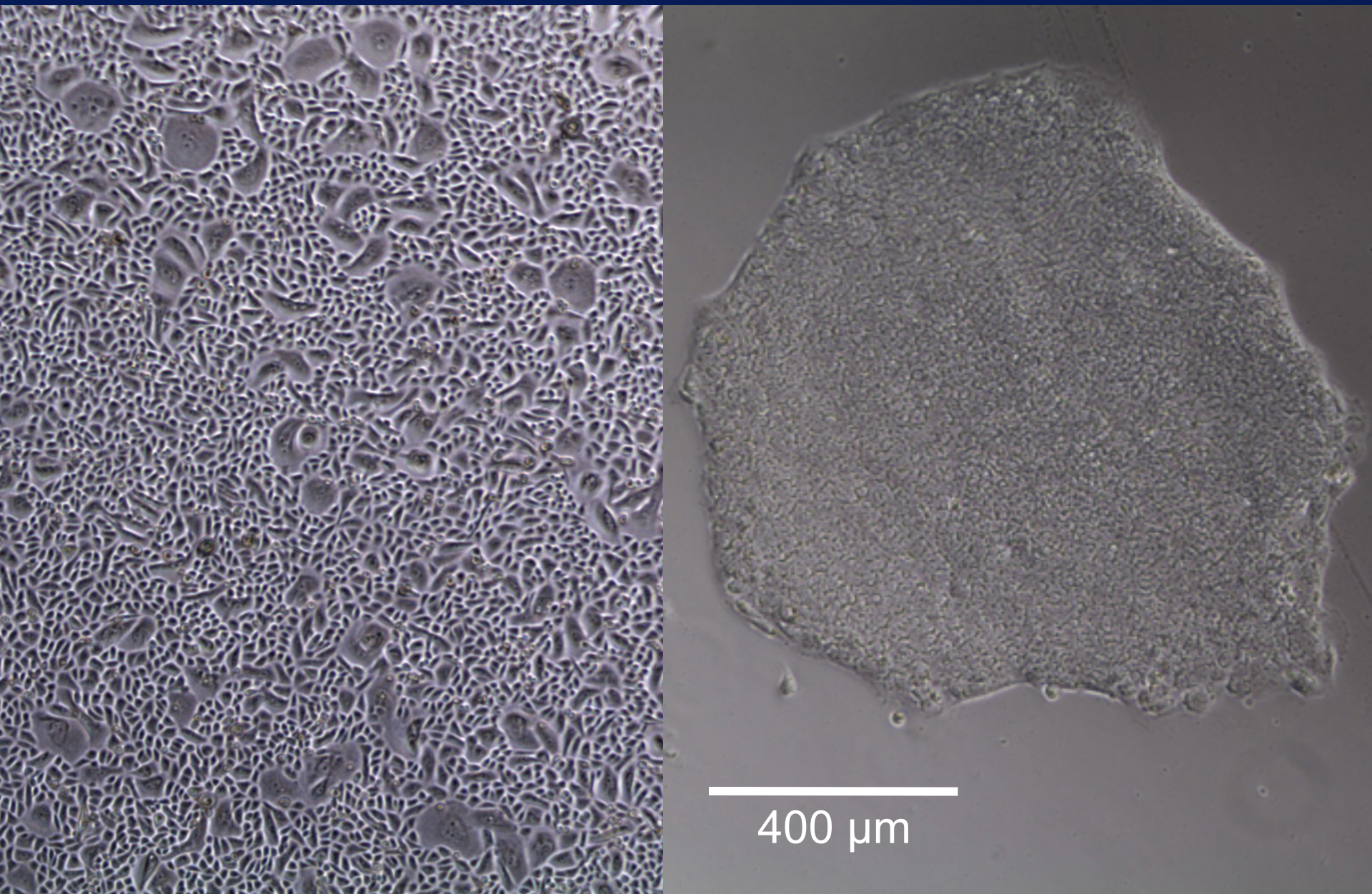
Keratinocytes

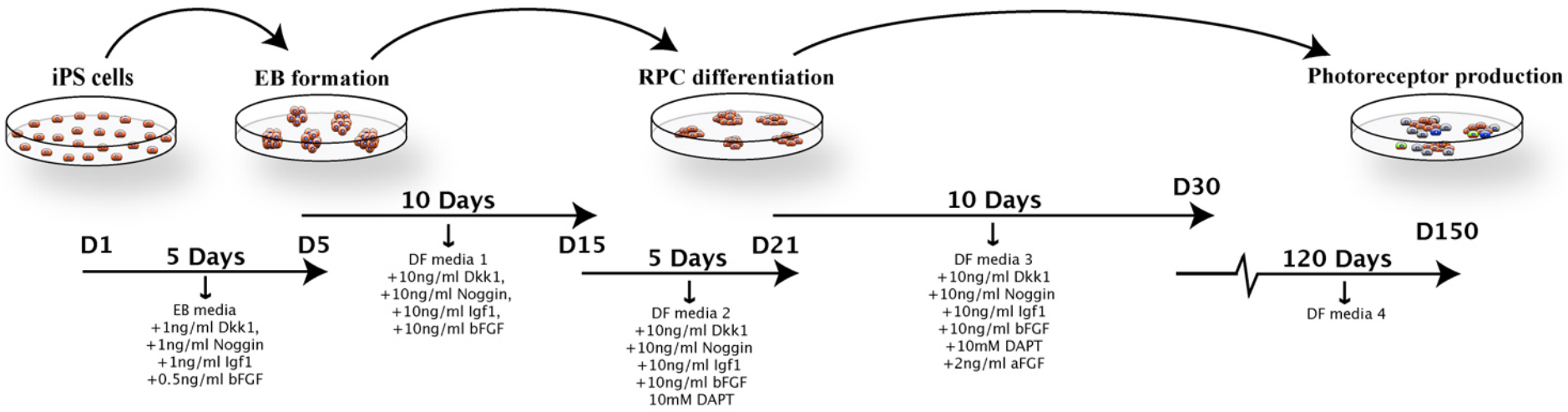


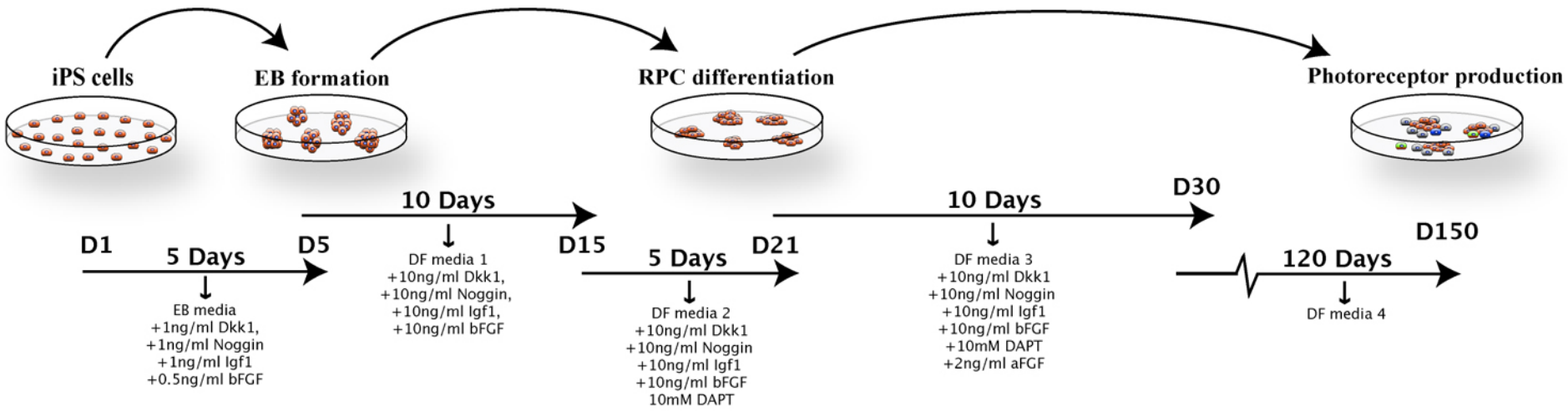
400 µm

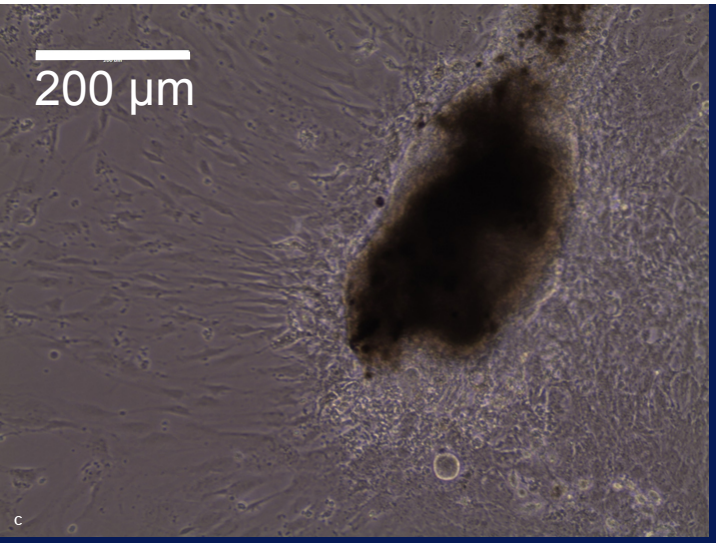
Keratinocytes

Isolated iPSCs

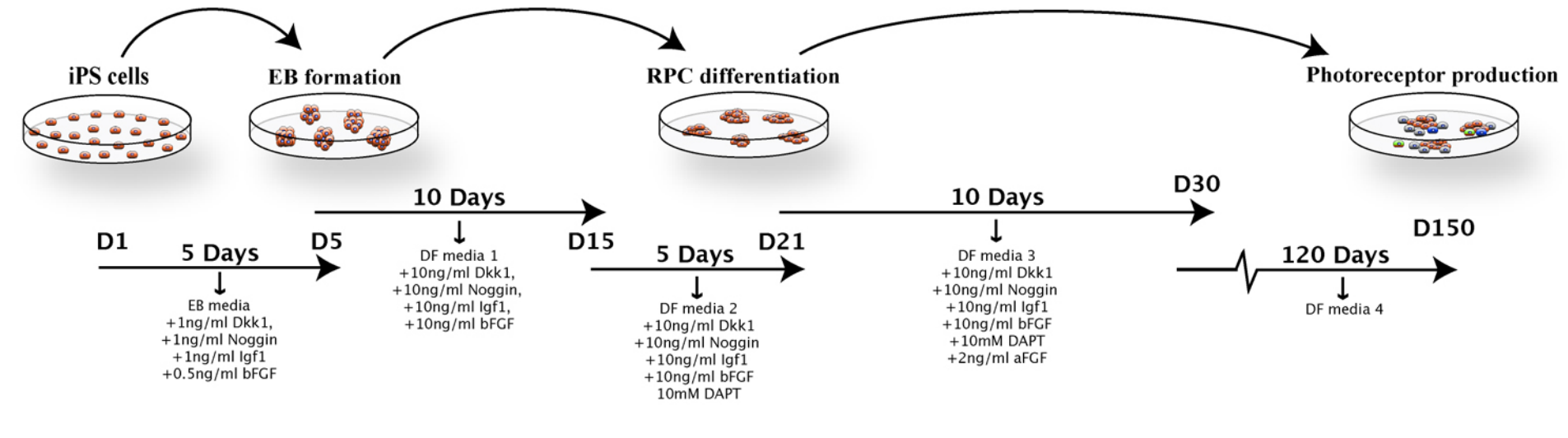


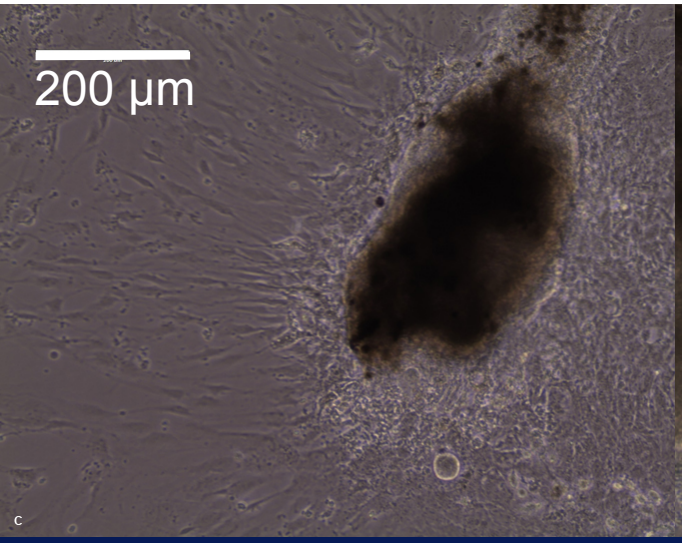

iPS cells
EB formation
RPC differentiation
Photoreceptor production
D1
5 Days
D5
EB media
+1ng/ml Dkk1,
+1ng/ml Noggin
+1ng/ml Igf1
+0.5ng/ml bFGF
10 Days
D15
DF media 1
+10ng/ml Dkk1,
+10ng/ml Noggin,
+10ng/ml Igf1,
+10ng/ml bFGF
5 Days
D21
DF media 2
+10ng/ml Dkk1
+10ng/ml Noggin
+10ng/ml Igf1
+10ng/ml bFGF
10mM DAPT
10 Days
D30
DF media 3
+10ng/ml Dkk1
+10ng/ml Noggin
+10ng/ml Igf1
+10ng/ml bFGF
+10mM DAPT
+2ng/ml aFGF
120 Days
D150
DF media 4

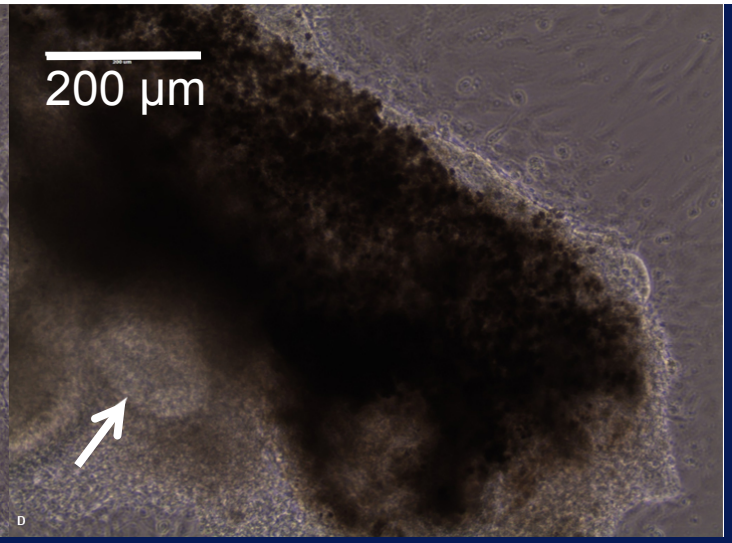

iPS cells
EB formation
RPC differentiation
Photoreceptor production
D1
5 Days
D5
EB media
+1ng/ml Dkk1,
+1ng/ml Noggin
+1ng/ml Igf1
+0.5ng/ml bFGF
10 Days
D15
DF media 1
+10ng/ml Dkk1,
+10ng/ml Noggin,
+10ng/ml Igf1,
+10ng/ml bFGF
5 Days
D21
DF media 2
+10ng/ml Dkk1
+10ng/ml Noggin
+10ng/ml Igf1
+10ng/ml bFGF
10mM DAPT
10 Days
D30
DF media 3
+10ng/ml Dkk1
+10ng/ml Noggin
+10ng/ml Igf1
+10ng/ml bFGF
+10mM DAPT
+2ng/ml aFGF
120 Days
D150
DF media 4


200 µm

45 days

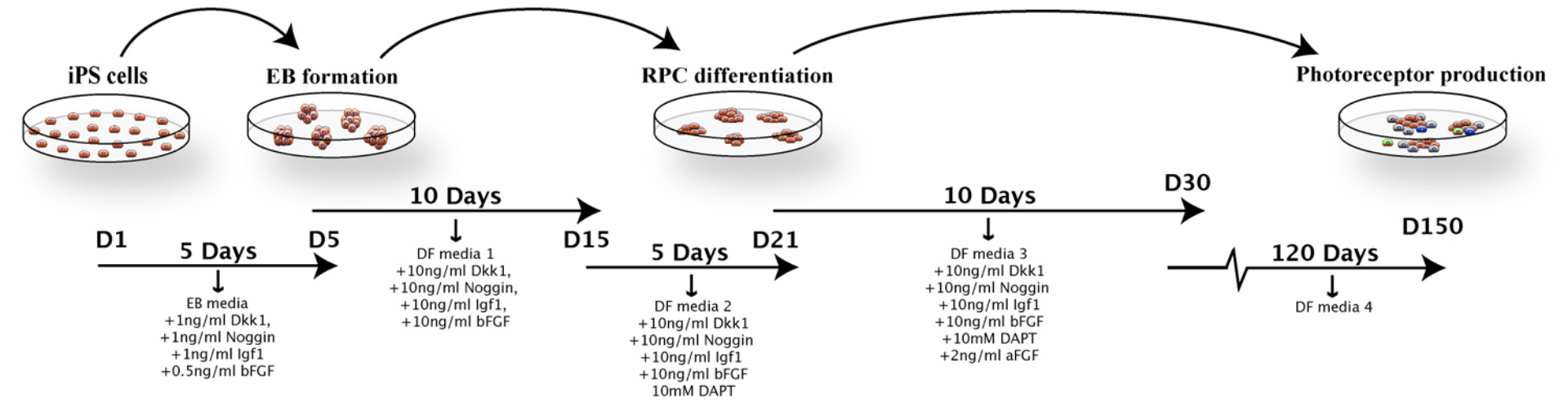


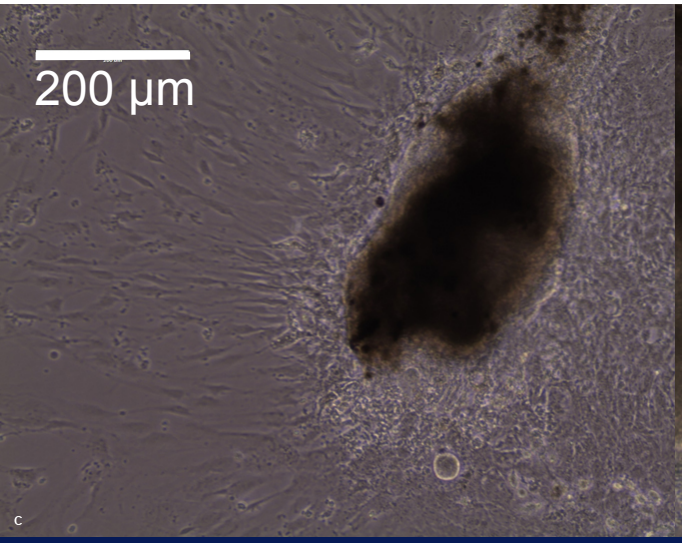


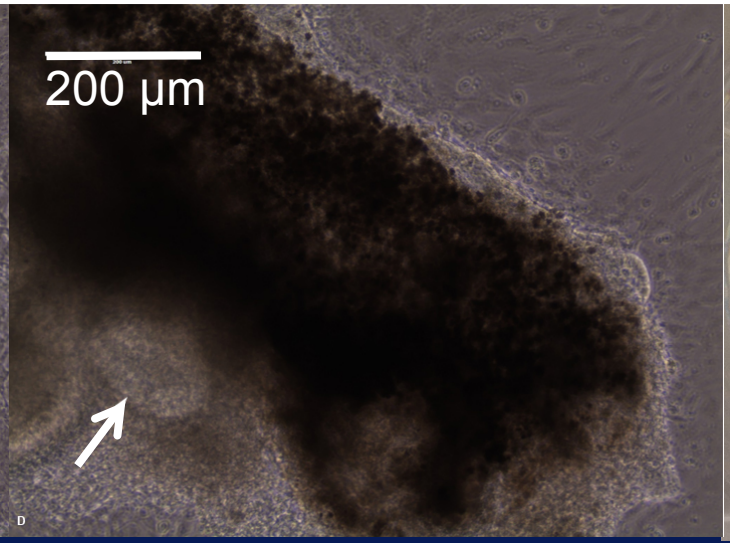


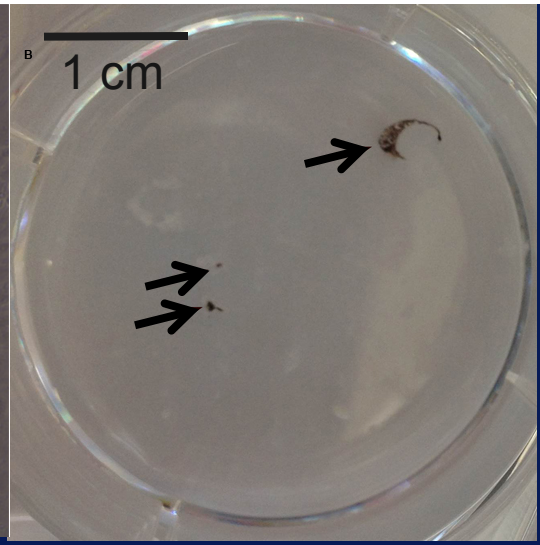
45 days

70 days





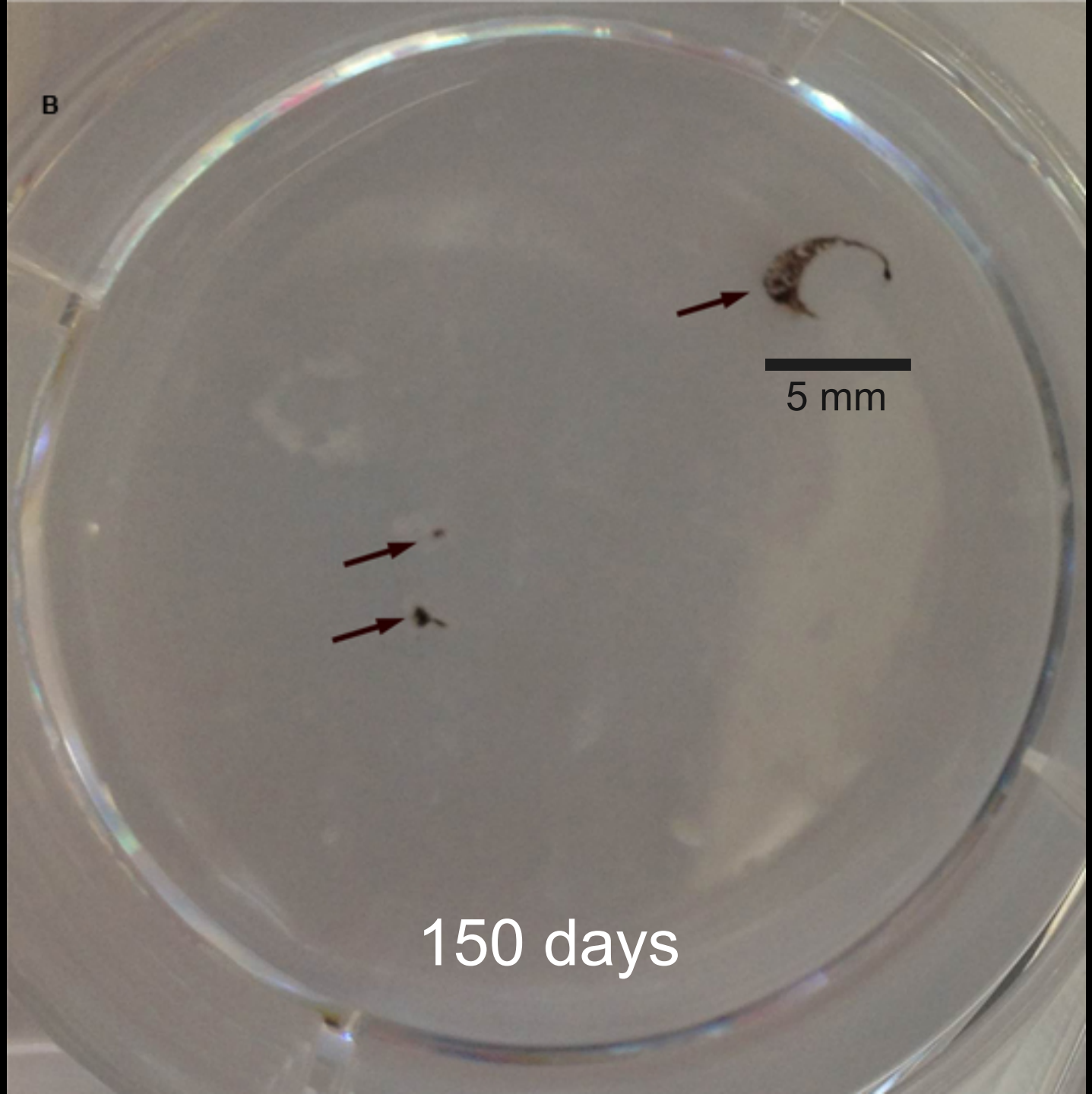




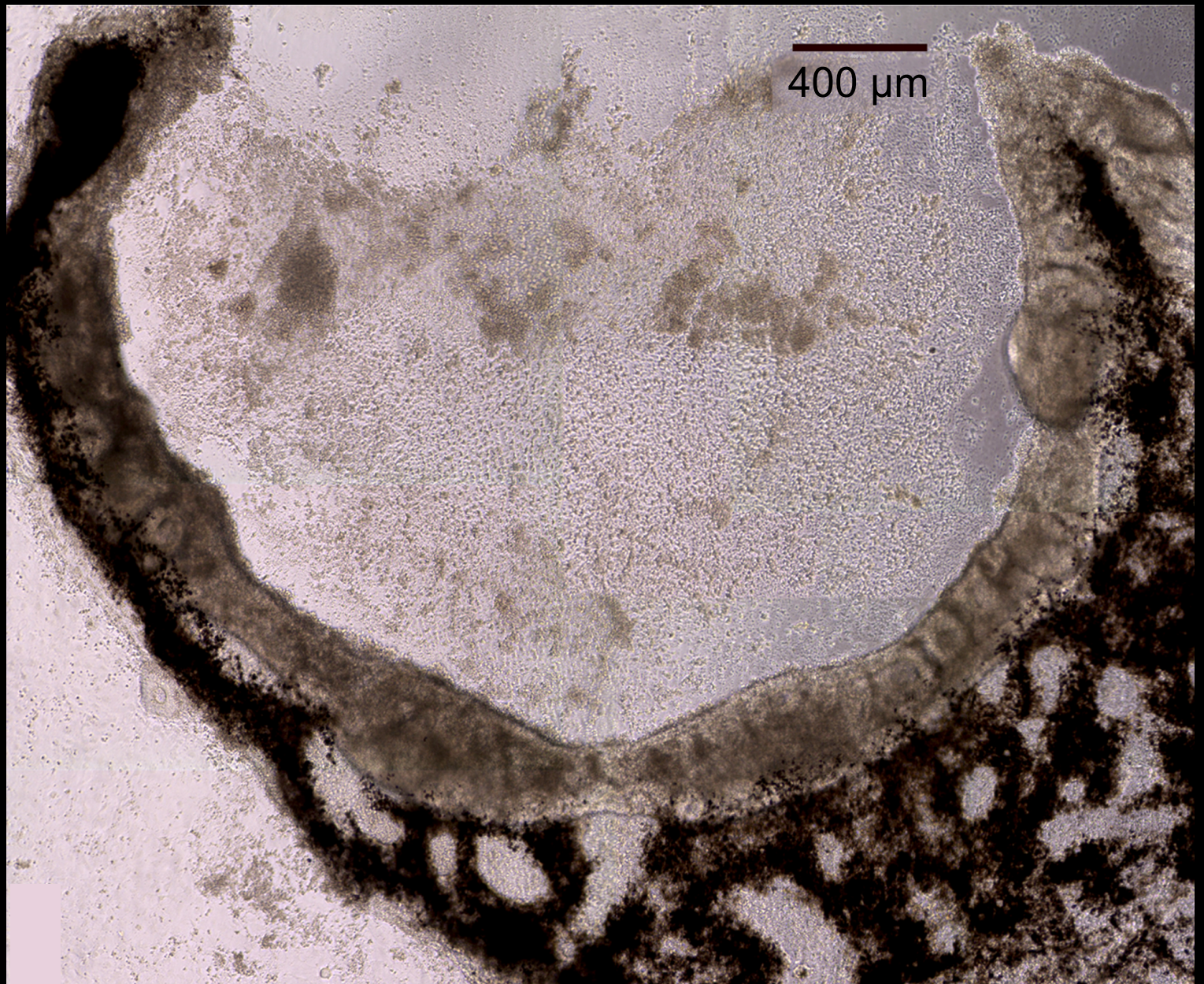
45 days

70 days

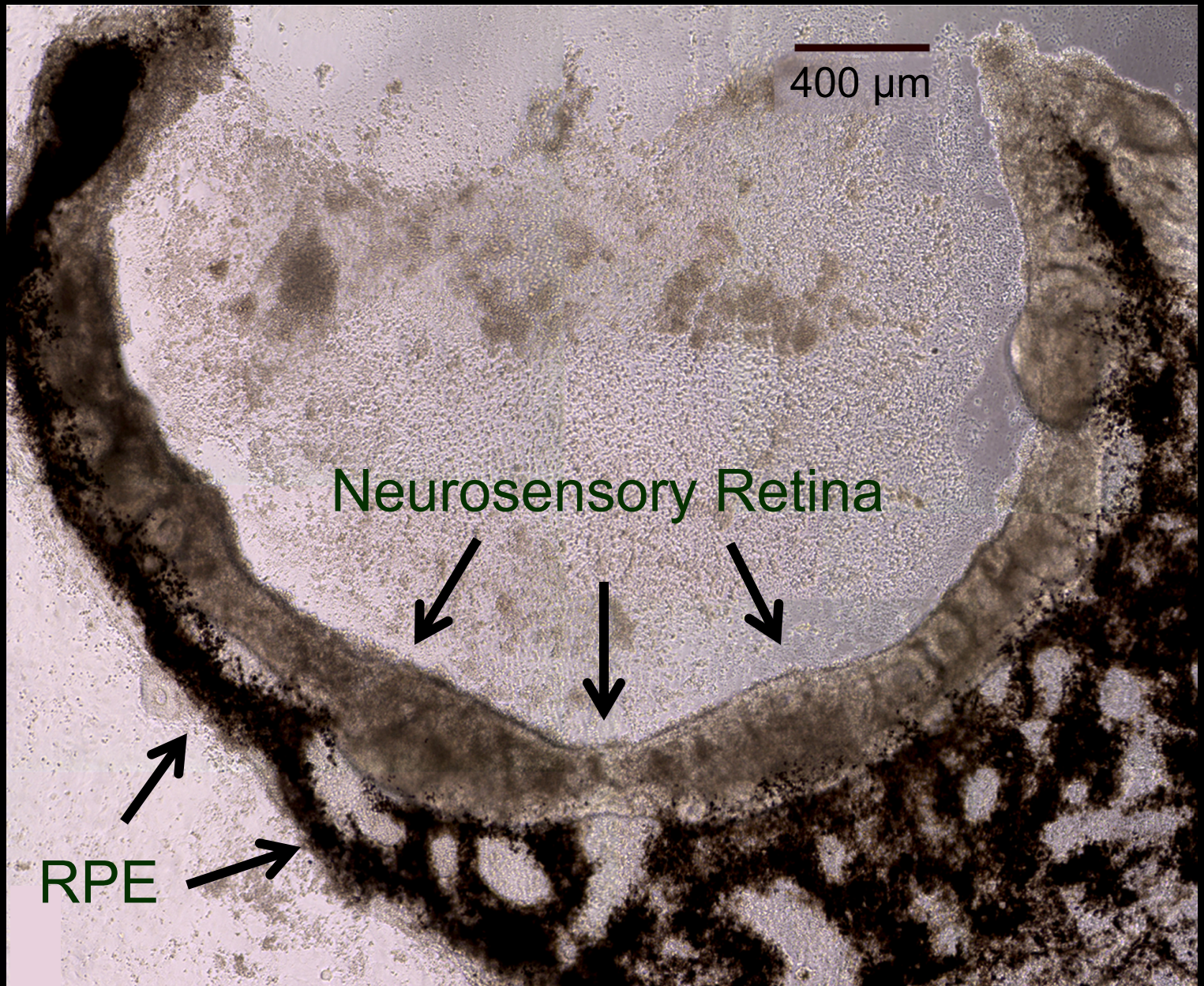
150 days


B
5 mm
150 days

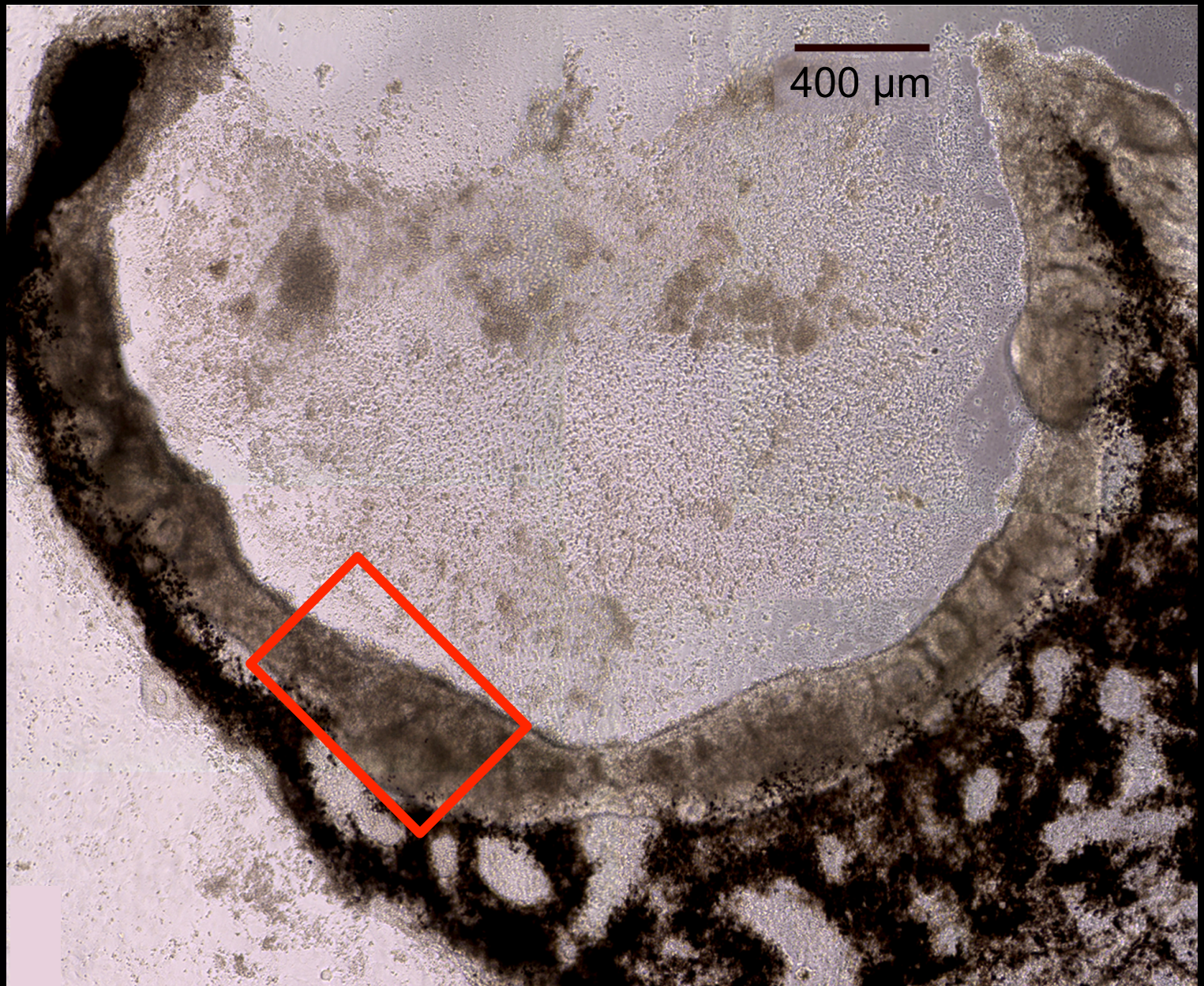
Multi-layer Eyecup-like Structure

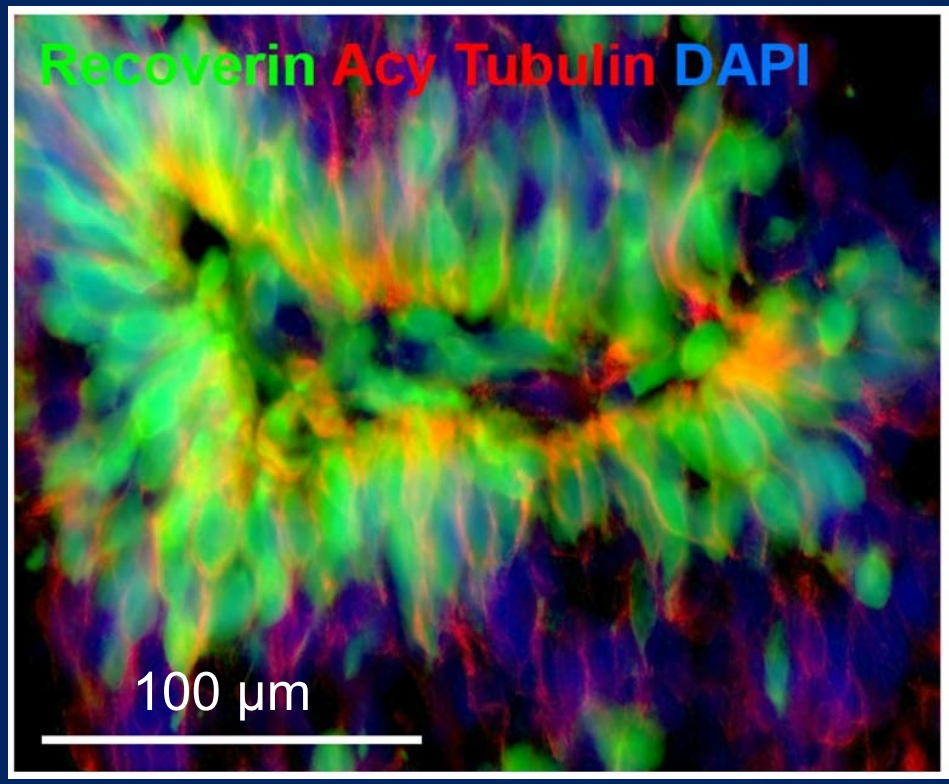


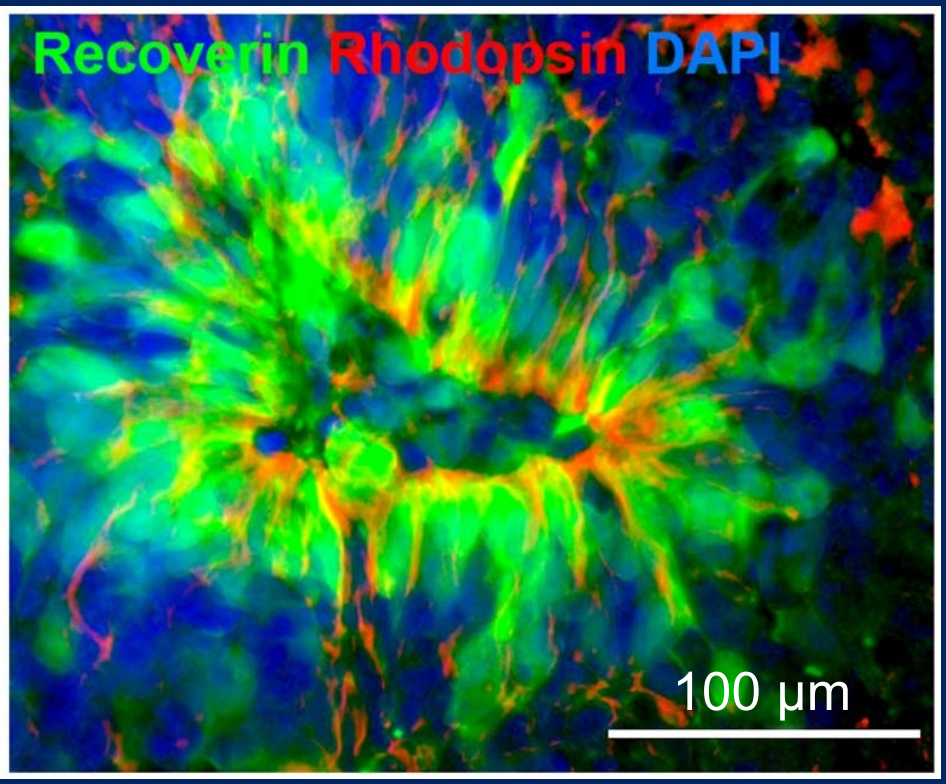
Multi-layer Eyecup-like Structure

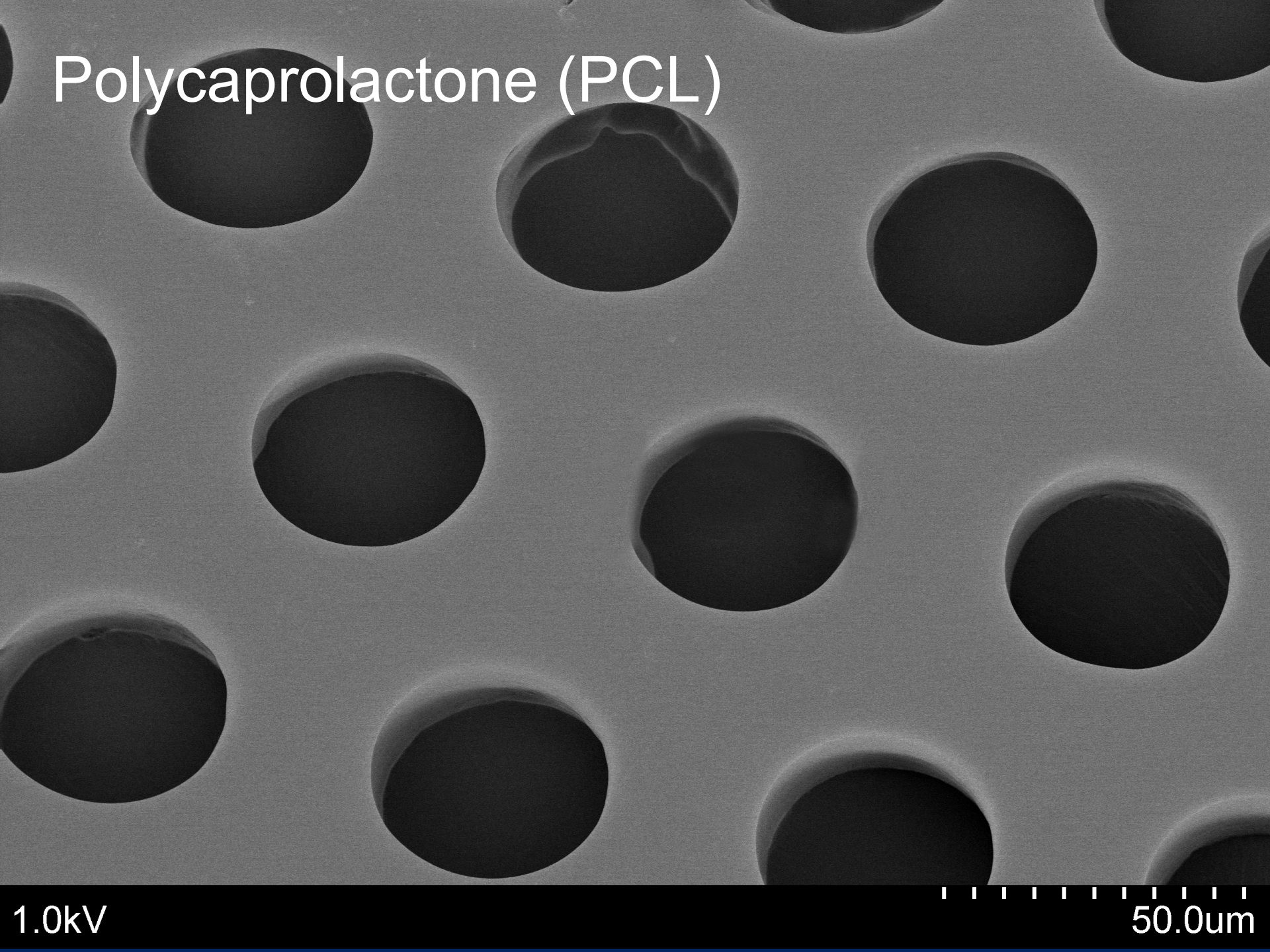


Multi-layer Eyecup-like Structure




Recoverin Acy Tubulin DAPI
100 µm


Recoverin Rhodopsin DAPI
100 µm


Polycaprolactone (PCL)
1.0kV
50.0um


500,000
cells

Parker Hannifin

DENSO

Cost?

Less than $50,000 (including ten years of follow up).

Imagine It!

- Gene therapies for all patients with early retinal disease.
- Stem cell based photoreceptor transplants for all patients with late stage photoreceptor disease.

How big are these goals?

Population Survey

- 1000 consecutive families with Mendelian retinal disease

Population Survey

- 1000 consecutive families with Mendelian retinal disease
- Causative mutations were found in 76% overall ($980 per family)

Population Survey

- 1000 consecutive families with Mendelian retinal disease
- Causative mutations were found in 76% overall ($980 per family)
- 104 different disease-causing genes in these 1000 families

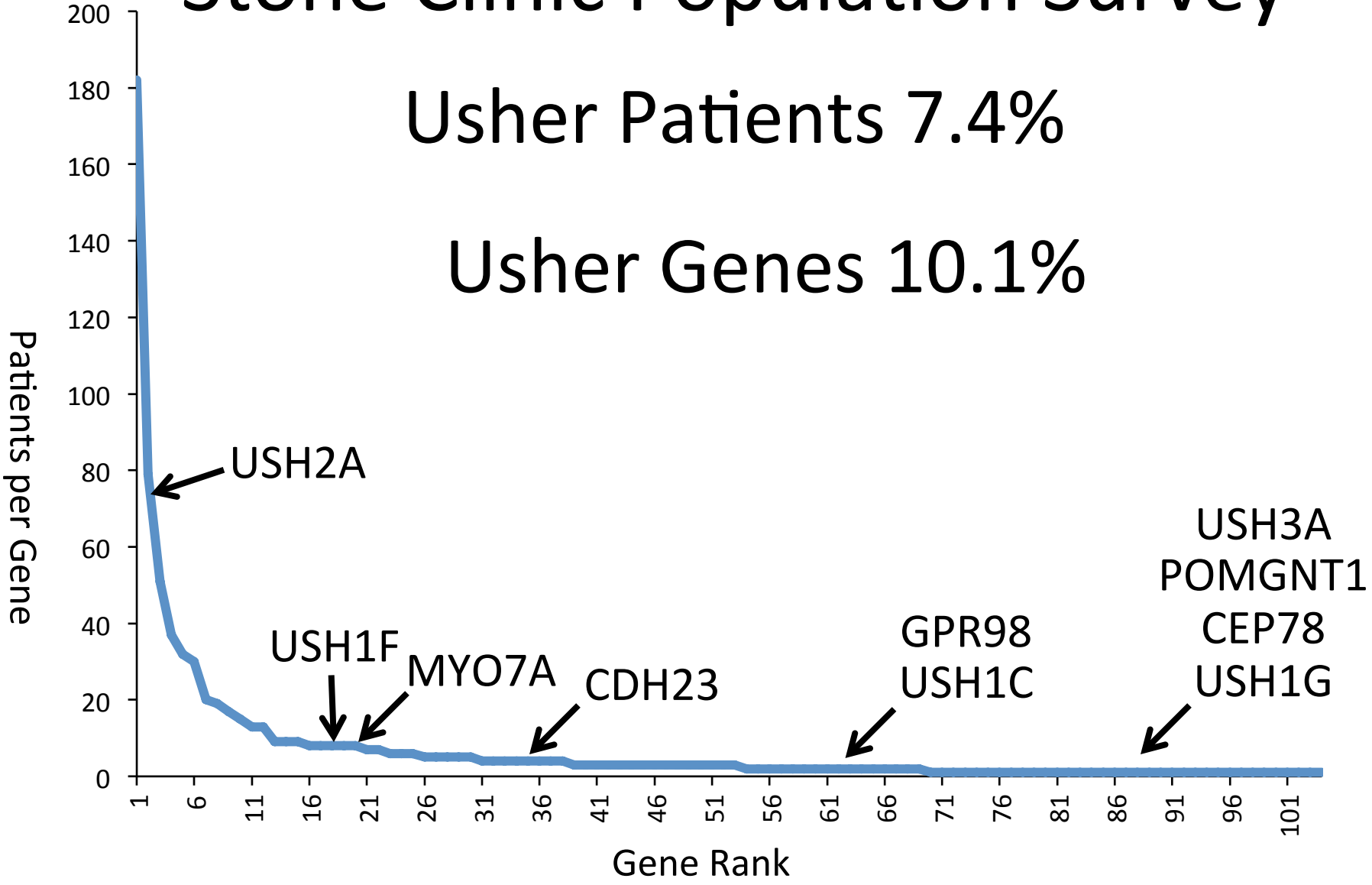
Population Survey

- 1000 consecutive families with Mendelian retinal disease
- Causative mutations were found in 76% overall ($980 per family)
- 104 different disease-causing genes in these 1000 families
- 10 Usher genes

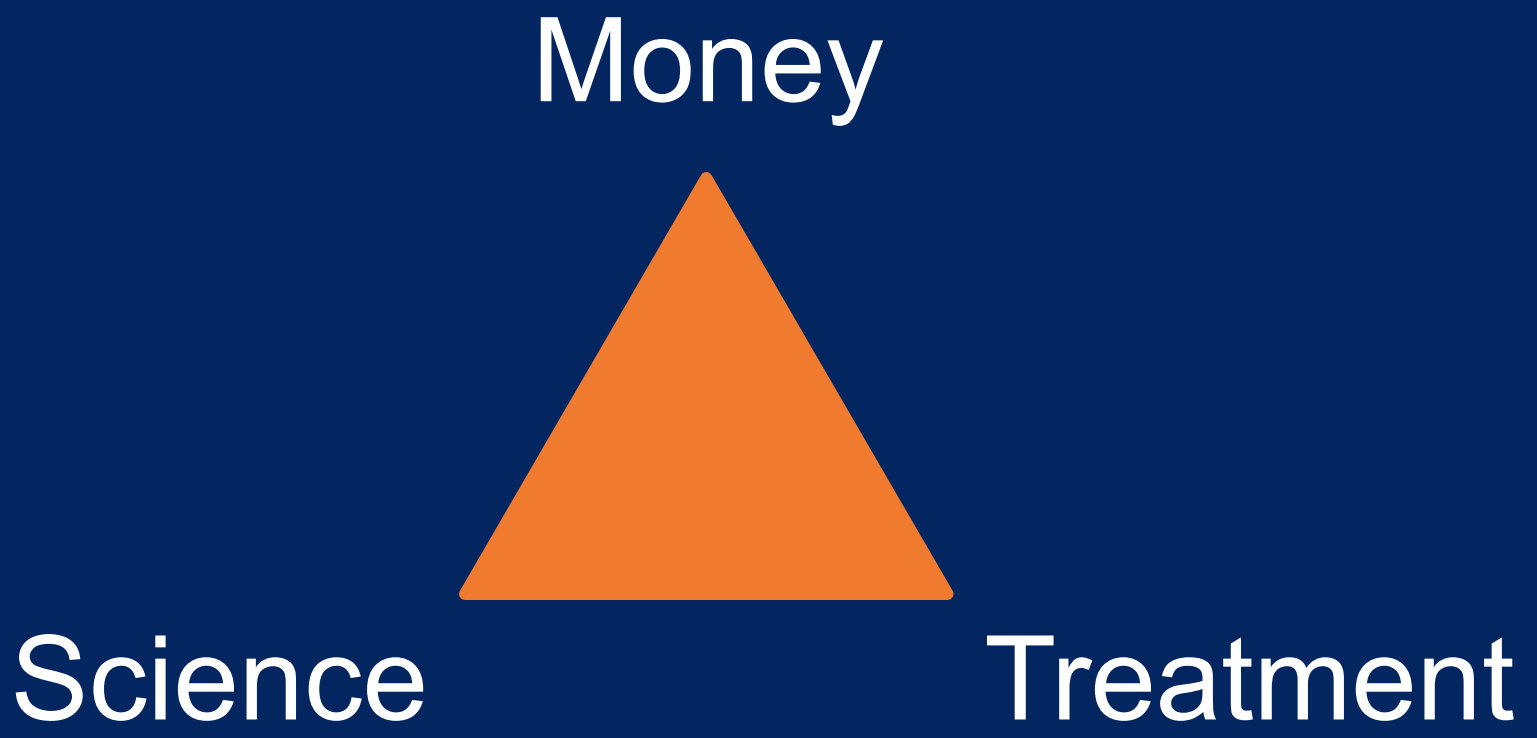
Stone Clinic Population Survey

Usher Patients 7.4%

Usher Genes 10.1%



Three Perspectives



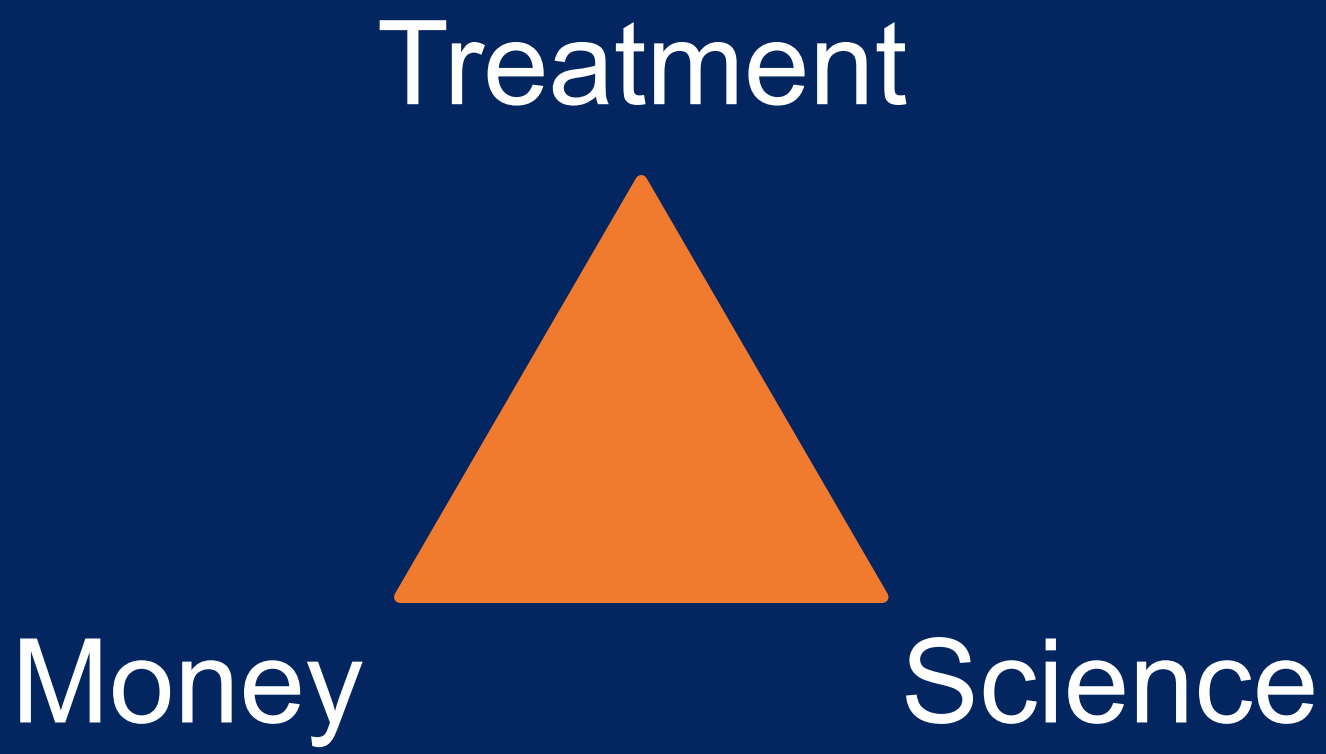
Three Perspectives

Science

Treatment

Money

Three Perspectives



Post Traumatic Stress Disorder

- You, a family member or close friend are suddenly and seriously injured

Post Traumatic Stress Disorder

- You, a family member or close friend are suddenly and seriously injured
- Anxiety, depression, poor sleep, uncontrollable thoughts

Post Traumatic Stress Disorder

- You, a family member or close friend are suddenly and seriously injured
- Anxiety, depression, poor sleep, uncontrollable thoughts
- Triggers (emails, phone calls, news stories, clinic visits, test results)

Post Traumatic Stress Disorder

- You, a family member or close friend are suddenly and seriously injured
- Anxiety, depression, poor sleep, uncontrollable thoughts
- Triggers (emails, phone calls, news stories, clinic visits, test results)
- Caregivers are also susceptible (compassion fatigue)

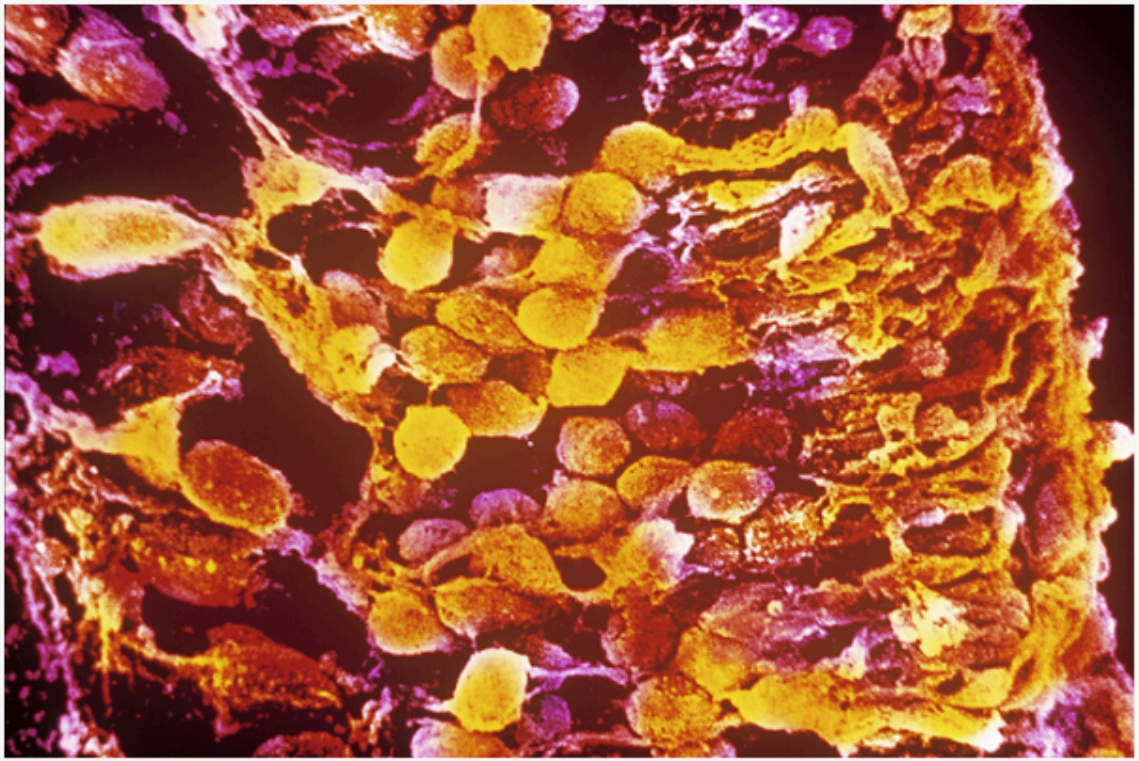
Three Recent Loud Noises
(none proved to be substantive)

- RIKEN suspends clinical trial
- Immunity to viruses may preclude eligibility for a trial
- CRISPR causes mutations

RIKEN suspends first clinical trial involving induced pluripotent stem cells

Ken Garber

Nature Biotechnology **33**, 890–891 (2015) | doi:10.1038/nbt0915-890
Published online 08 September 2015



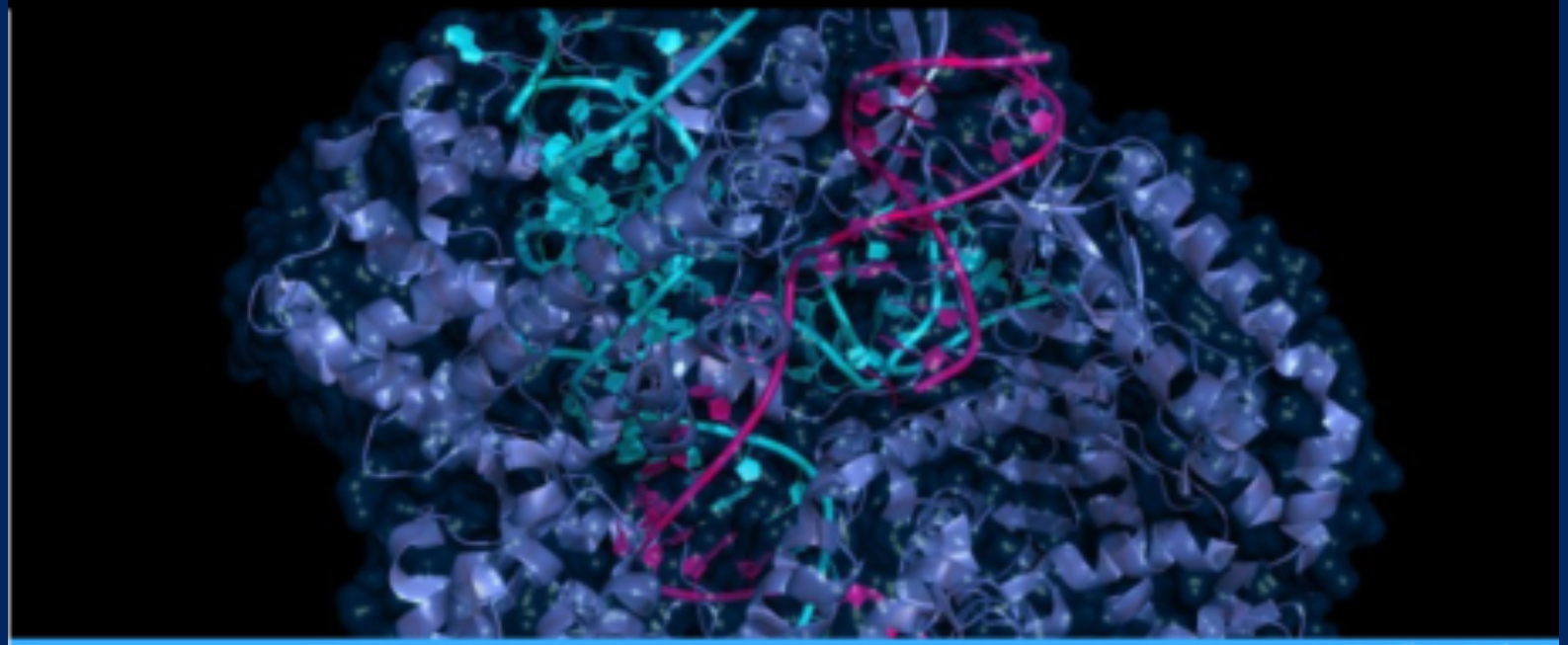
CHNO LIOTET / Science Source

The human eye retina is formed from numerous layers, with the retinal pigment epithelium forming a layer on top.

Altered virus could help more patients to become eligible for human gene therapy trials

Download PDF Copy

June 13, 2017



petarg/Shutterstock.com

CRISPR Gene-Editing Can Cause Hundreds of Unexpected Mutations

Uh oh...

BEC CREW 30 MAY 2017

It's been hailed as one of the most potentially transformative inventions in modern medicine, bringing the prospect of designer babies closer than any other technology to date, but CRISPR-Cas9 could be riskier than we thought.

The technology that could spark a gene-editing revolution has been caught introducing hundreds of unintended mutations into the genome, and with scientists already testing it in humans, it's set off some serious alarm bells.

This story had an immediate effect on stock prices.

Editas Medicine (NASDAQ:EDIT)	↓ 15.7%
CRISPR Therapeutics (NASDAQ:CRSP)	↓ 6.9%
Intellia Therapeutics (NASDAQ:NTLA)	↓ 14.9%

This story had an immediate effect on stock prices.

Editas Medicine (NASDAQ:EDIT)	↓ 15.7%
CRISPR Therapeutics (NASDAQ:CRSP)	↓ 6.9%
Intellia Therapeutics (NASDAQ:NTLA)	↓ 14.9%

Millions of dollars changed hands because of three mice.

Reaction was swift and negative.

- This is a terrible paper and as a reviewer I would have dismissed it from the first round of review.
- I found stunning this paper got so widely promoted on such unsubstantiated claims, all based on the media release piece only.

  -- Gaetan Burgio, JCSMR

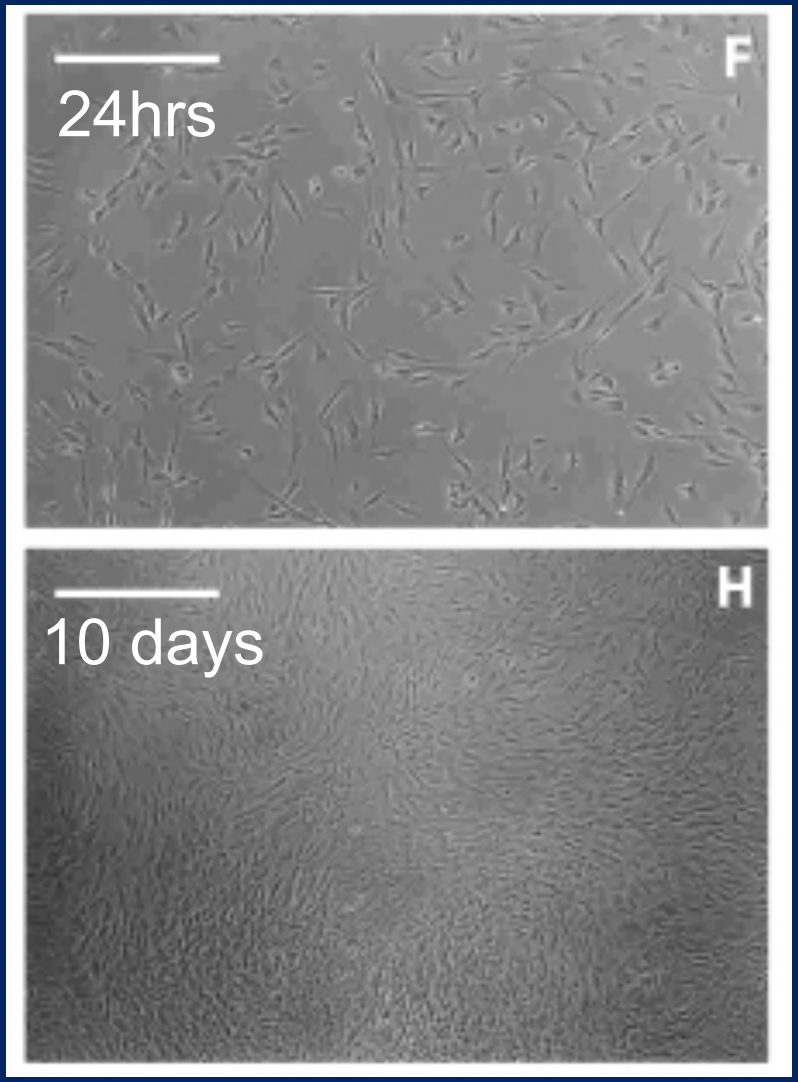
But, what if . . .?

But, what if . . .?

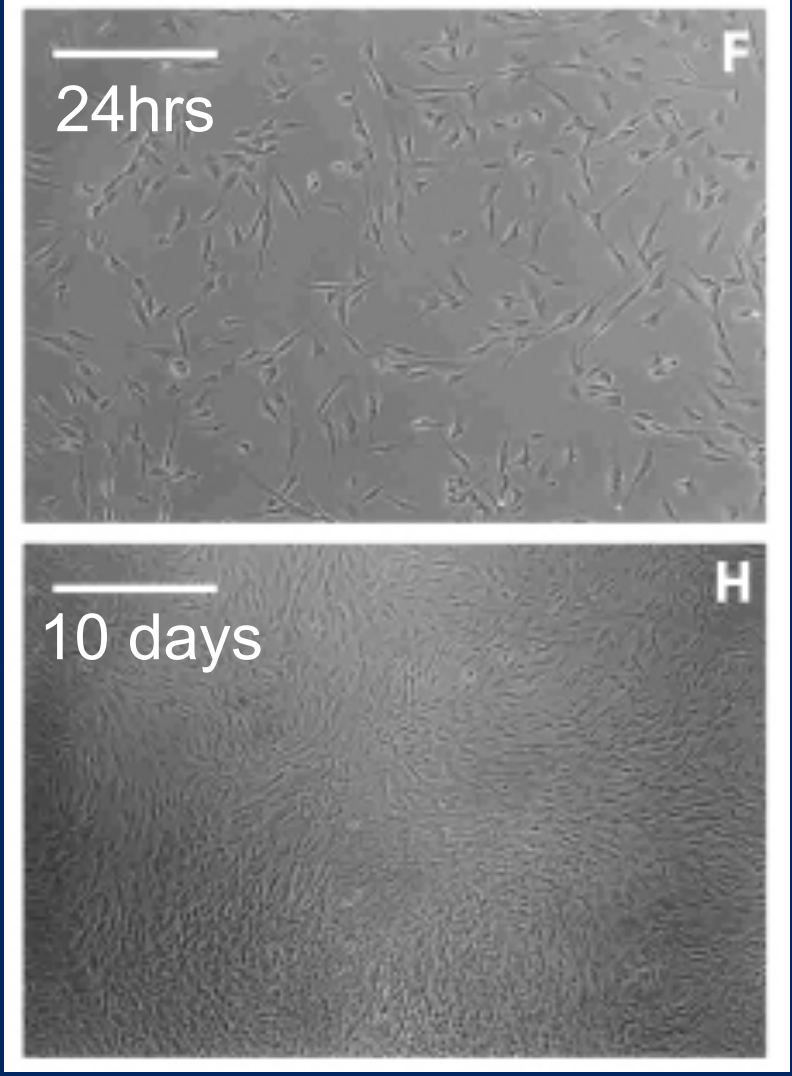
We will fix it.

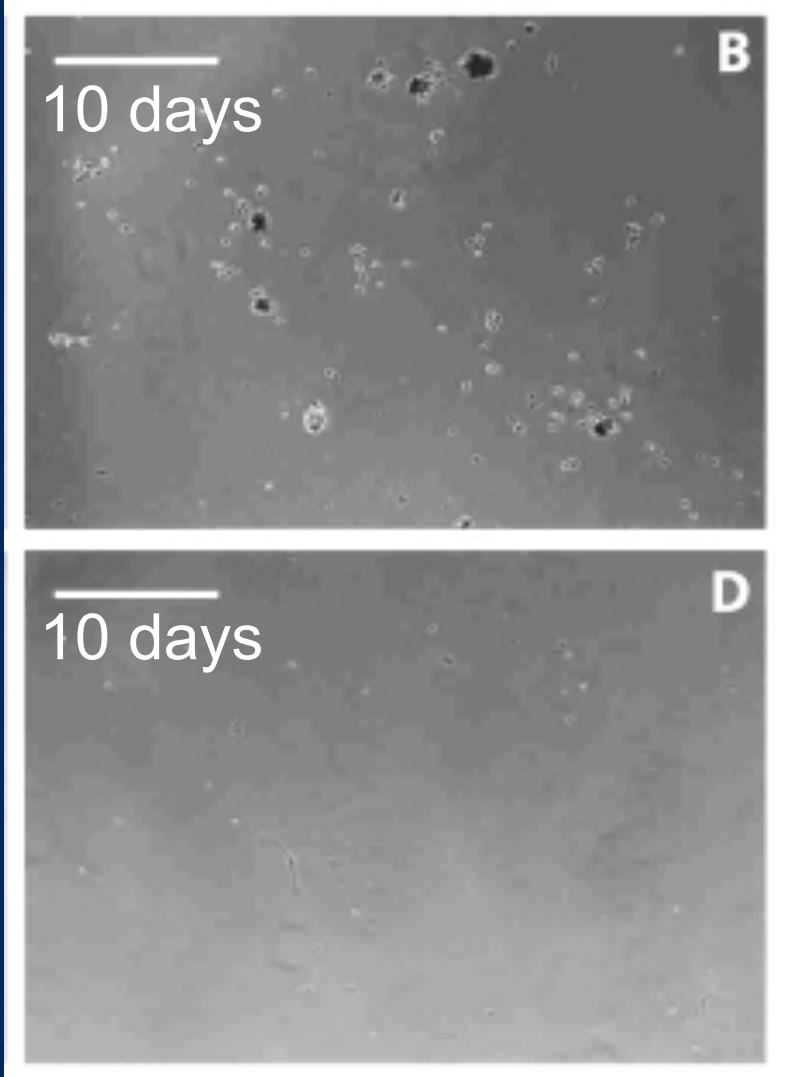
A Problem You Didn’t Hear About

A Problem You Didn't Hear About



A Problem You Didn't Hear About

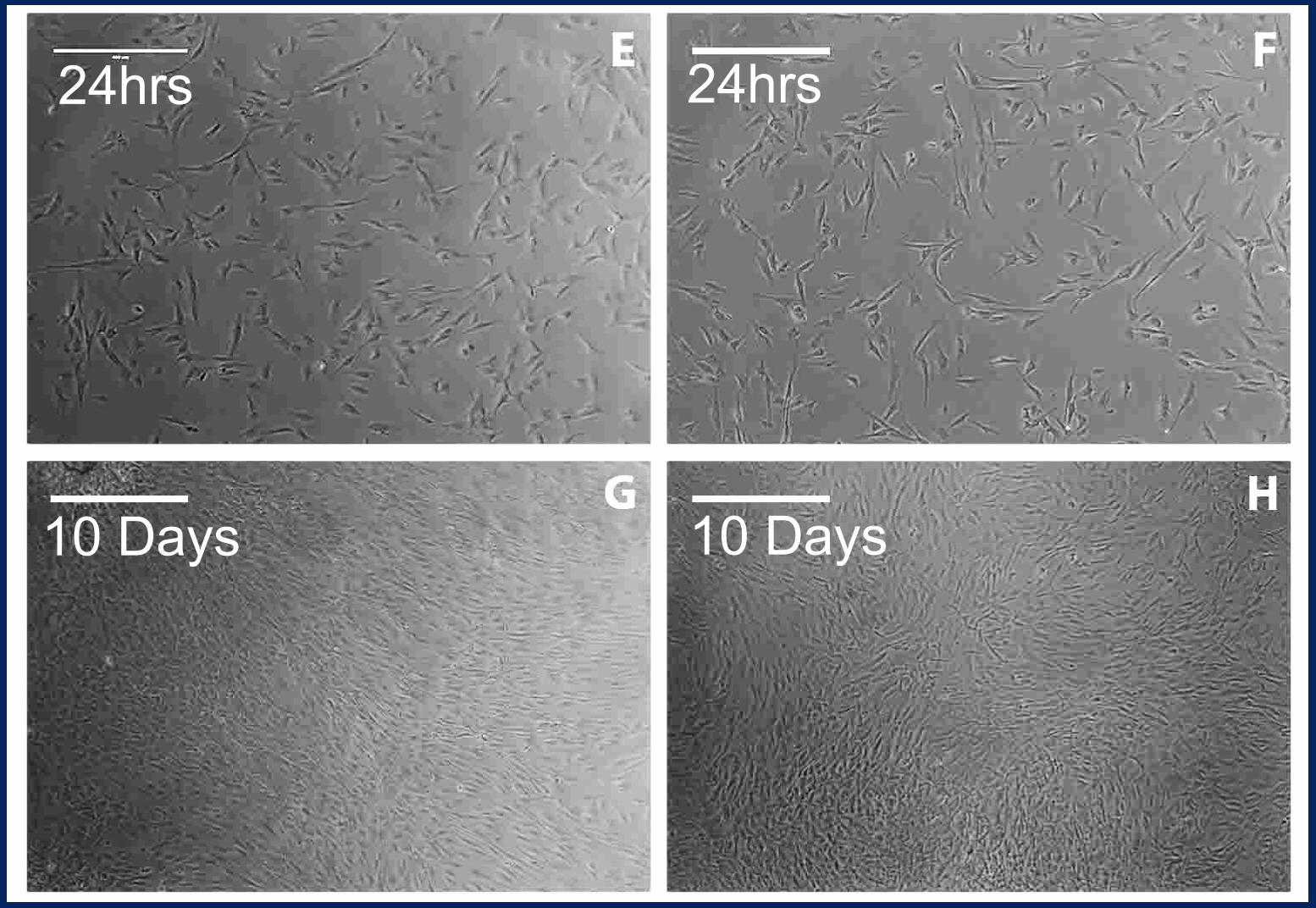




A Problem You Didn't Hear About

Patient	Age	Sex	FibroGRO™
T3	29	Male	++
T2	36	Male	+
T1	47	Male	+
T7	56	Male	-
T4	61	Male	-
T6	79	Female	-
T5	81	Male	-

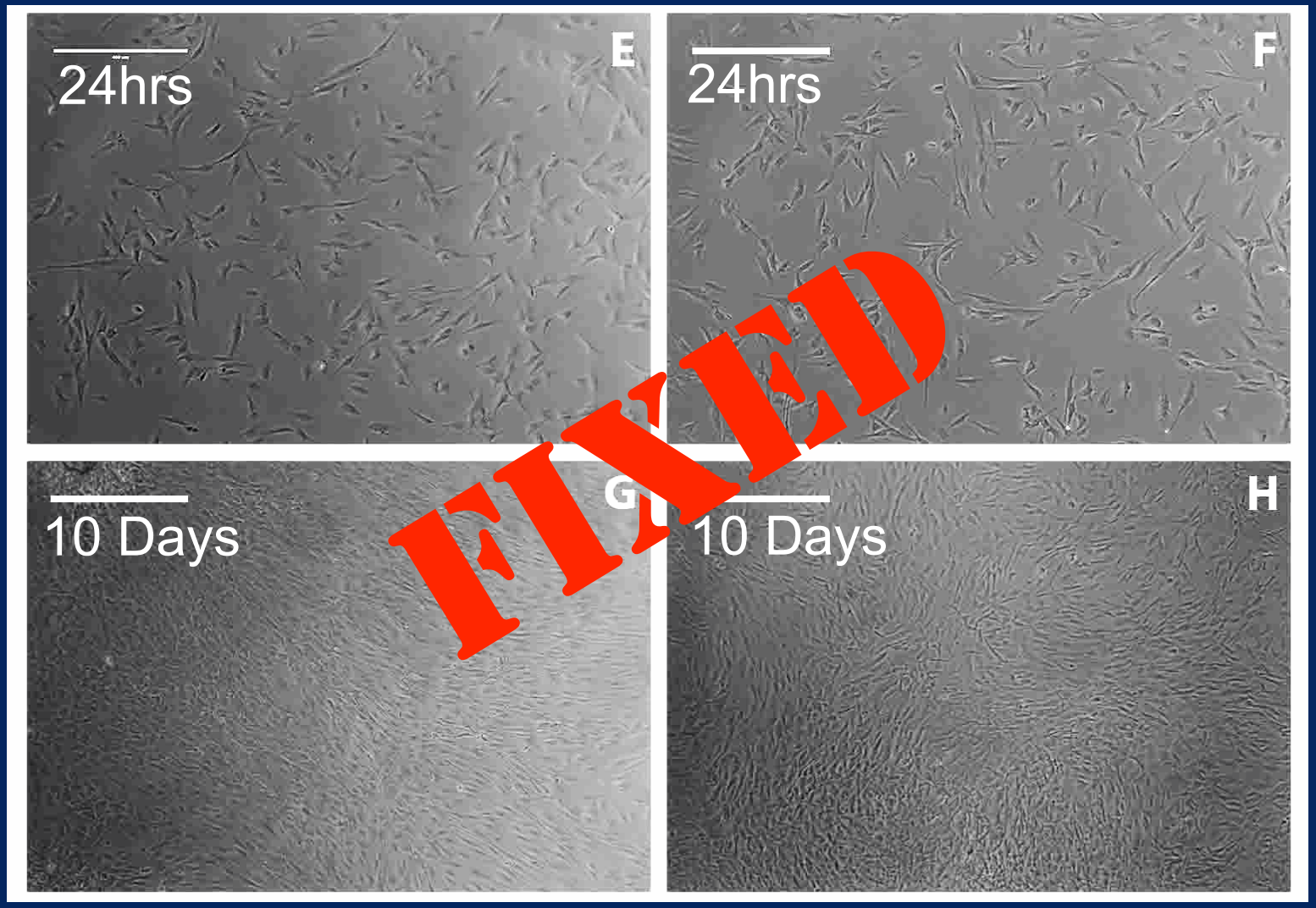
A Problem You Didn't Hear About



74 years old

81 years old

Wiley, et al., Scientific Reports, 2016.



Our Path to the Cures

Our Path to the Cures

- Work primarily within a nonprofit, philanthropic culture.

Our Path to the Cures

- Work primarily within a nonprofit, philanthropic culture.
- Share ideas freely; publish quickly, share detailed methodology when asked.

Our Path to the Cures

- Work primarily within a nonprofit, philanthropic culture.
- Share ideas freely; publish quickly, share detailed methodology when asked.
- Leave no one behind; work on lots of different diseases (early and late stages) and lots of different genes at the same time.

Our Path to the Cures

- Reduce waste; avoid detailed annual reports, institutional overhead, and unnecessary administrative layers.

Our Path to the Cures

- Reduce waste; avoid detailed annual reports, institutional overhead, and unnecessary administrative layers.
- Confine discussions of progress and plans to published papers, formal scientific presentations.

Our Path to the Cures

- Reduce waste; avoid detailed annual reports, institutional overhead, and unnecessary administrative layers.
- Confine discussions of progress and plans to published papers, formal scientific presentations.
- Replace animal models with cultured cells whenever possible; use cells for efficacy, animals for safety.

Our Path to the Cures

- Reduce the cost and improve the sensitivity of genetic tests, so that one can find patients who might wish to join trials and, find the remaining disease-causing genes.

Our Path to the Cures

- Reduce the cost and improve the sensitivity of genetic tests, so that one can find patients who might wish to join trials and, find the remaining disease-causing genes.
- Develop philanthropically funded GMP facilities to reduce the costs of therapeutic vectors and cells.

Our Path to the Cures

- Develop reusable gene therapy strategies, especially genome editing methods for large and/or expression-sensitive genes.

Our Path to the Cures

- Develop reusable gene therapy strategies, especially genome editing methods for large and/or expression-sensitive genes.
- Develop cell therapies based upon patient-derived stem cells, to reduce the risk of immune rejection.

Our Path to the Cures

- Develop reusable gene therapy strategies, especially genome editing methods for large and/or expression-sensitive genes.
- Develop cell therapies based upon patient-derived stem cells, to reduce the risk of immune rejection.
- Analyze existing clinical data to determine the best timing and anatomic location for therapy.

BOYS TOWN
National Research Hospital

March 16, 2016

Dear Mr. Lebsack,

We are writing to you because of your previous participation in research studies of Usher Syndrome led by Dr. Bill Kimberling at the Boys Town National Research Hospital. We are happy to report that this research is still ongoing and that there has been a lot of great progress in recent years.

Dr. Kimberling has recently retired after a tremendously successful career spanning more than 40 years. In recognition of Bill's many contributions to Usher Syndrome Research, the University of Iowa has created the William Kimberling Usher Research Laboratory to continue pursuing treatments and cures for this serious condition. This laboratory was made possible by a very generous contribution from Mr. Howard Ruby, a California businessman, photographer, environmentalist and philanthropist, who is himself affected by retinitis pigmentosa caused by an Usher gene. Going forward, the Kimberling Laboratory at the University of Iowa will assume responsibility for distributing the results of Dr. Kimberling's research studies to individual study participants who are interested in them. If you would like to find out what has been found from the study of any blood samples you may have provided to Dr. Kimberling in the past, please contact the new Kimberling Laboratory at

usher-lab@uiowa.edu or 319-335-8270

and a member of the lab will work with you to update you on the status of the research. If there are any positive findings in your sample, the lab will work with you to get a written report of the findings that your doctor can review with you. You can learn more about the Kimberling Laboratory by visiting their website:

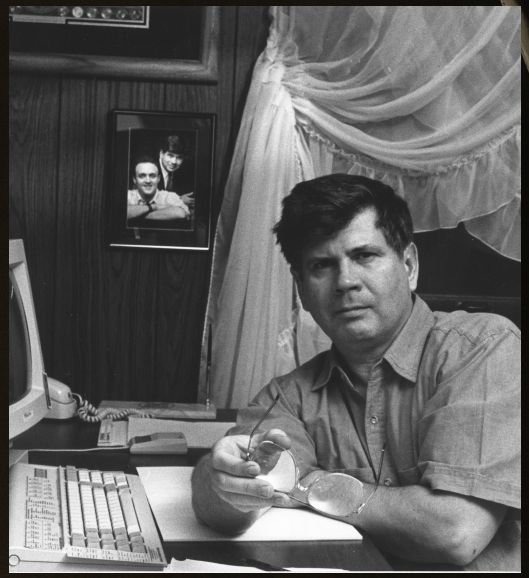
www.ProjectUsher.org.

555 North 30th Street
Omaha, Nebraska 68131
(402) 498-6511

14000 Boys Town Hospital Road
Boys Town, Nebraska 68010
(402) 778-6000

boystownhospital.org

Saving Children, Healing Families



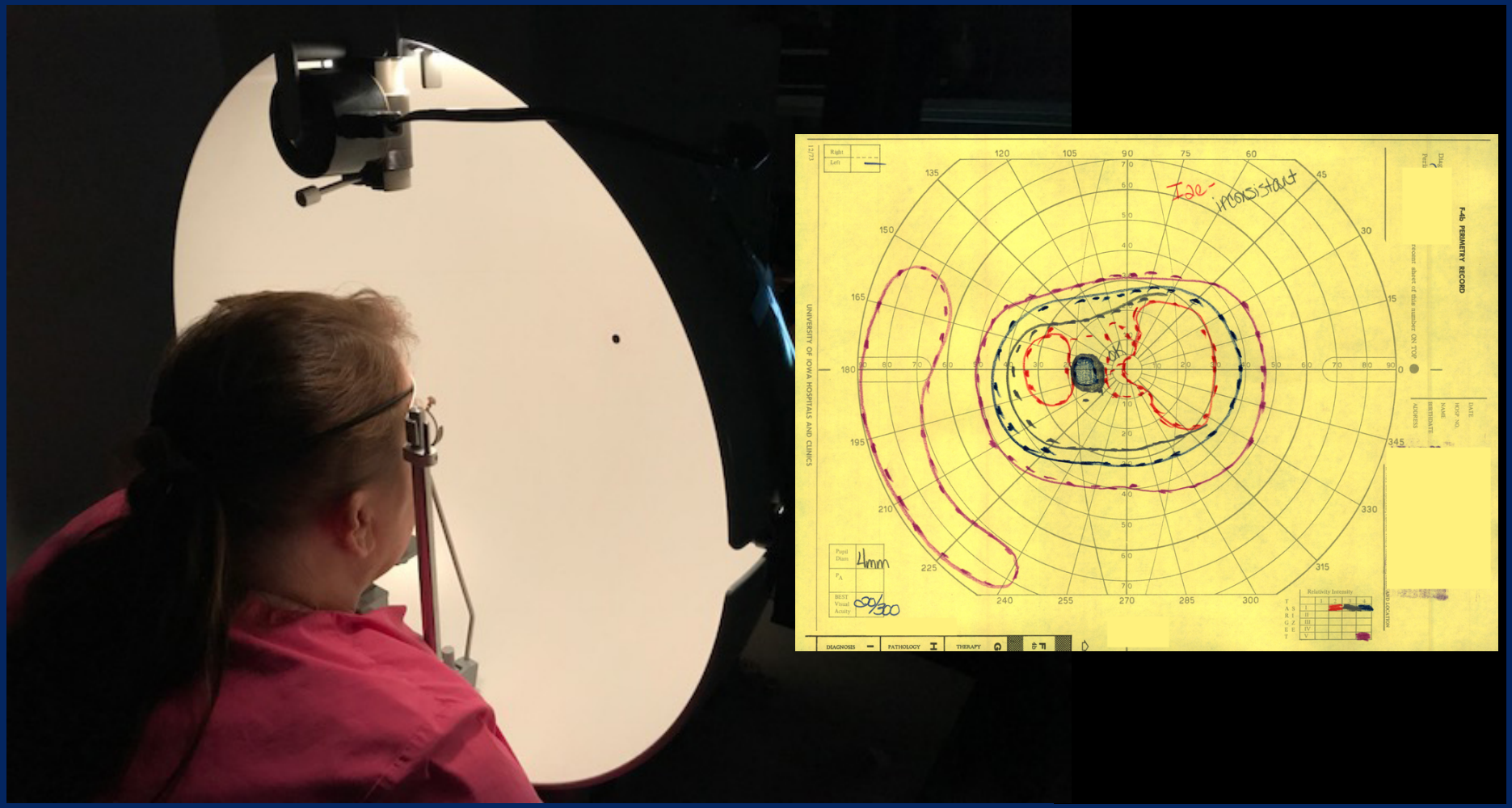
Usher Cohort
2207 patients, 1765 families

- William Kimberling
- Sam Jacobson
- Jerry Fishman
- Richard Weleber
- Elias Traboulsi
- Elise Heon
- Byron Lam
- Claes Moller
- Sten Andreasson
- Alex Levin
- Christine Kay
- Raymond Iezzi
- Mina Chung
- Alessandro Iannaccone

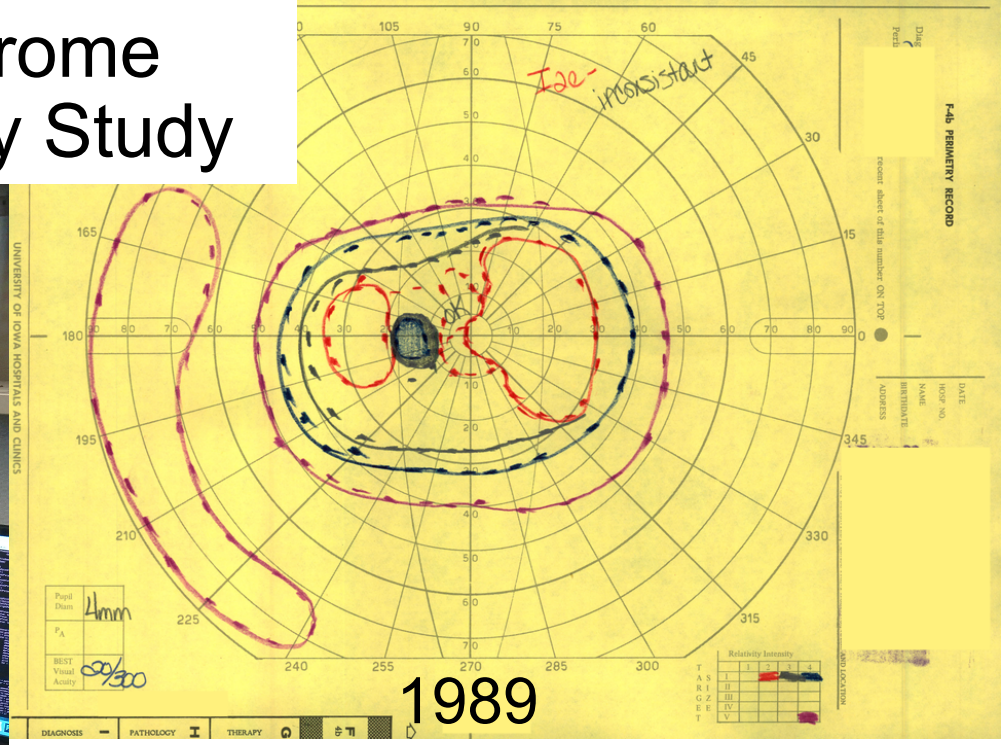
Usher Cohort
2207 patients, 1765 families

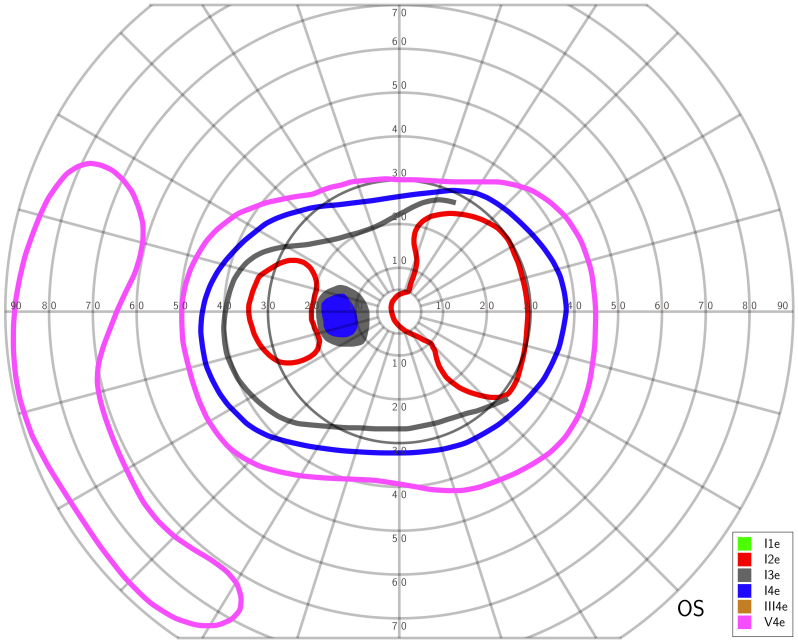
- USH2A 609
- MYO7A (1B) 249
- CDH23 (1D) 68
- USH3A 43
- PCDH15 (1F) 28
- USH1C 30
- GPR98 (2C) 10
- USH1G 1

Goldmann Perimetry



Usher Syndrome Natural History Study





Our Path to the Cures

- Focus almost entirely on Phase I-II clinical trials with long but fairly conventional follow-up.

Our Path to the Cures

- Focus almost entirely on Phase I-II clinical trials with long but fairly conventional follow-up.
- View every aspect of our work from the perspective of the clinical outcomes we want (and the realities of the diseases we are facing) instead of the perspectives of financial benefit, customary practice, or personal convenience.

Our Path to the Cures

- Do everything with a sense of URGENCY.

Summary

- Positive thinking (realistic hope)
- Leave no one behind
- Genetic testing – < $1000
- Gene therapy – < $20,000
- Stem cell therapy – < $50,000

Acknowledgements

Budd Tucker, Rob Mullins, Luke Wiley, Ian Han, Elliott Sohn, Steve Russell.

Stephen A. Wynn Institute for Vision Research