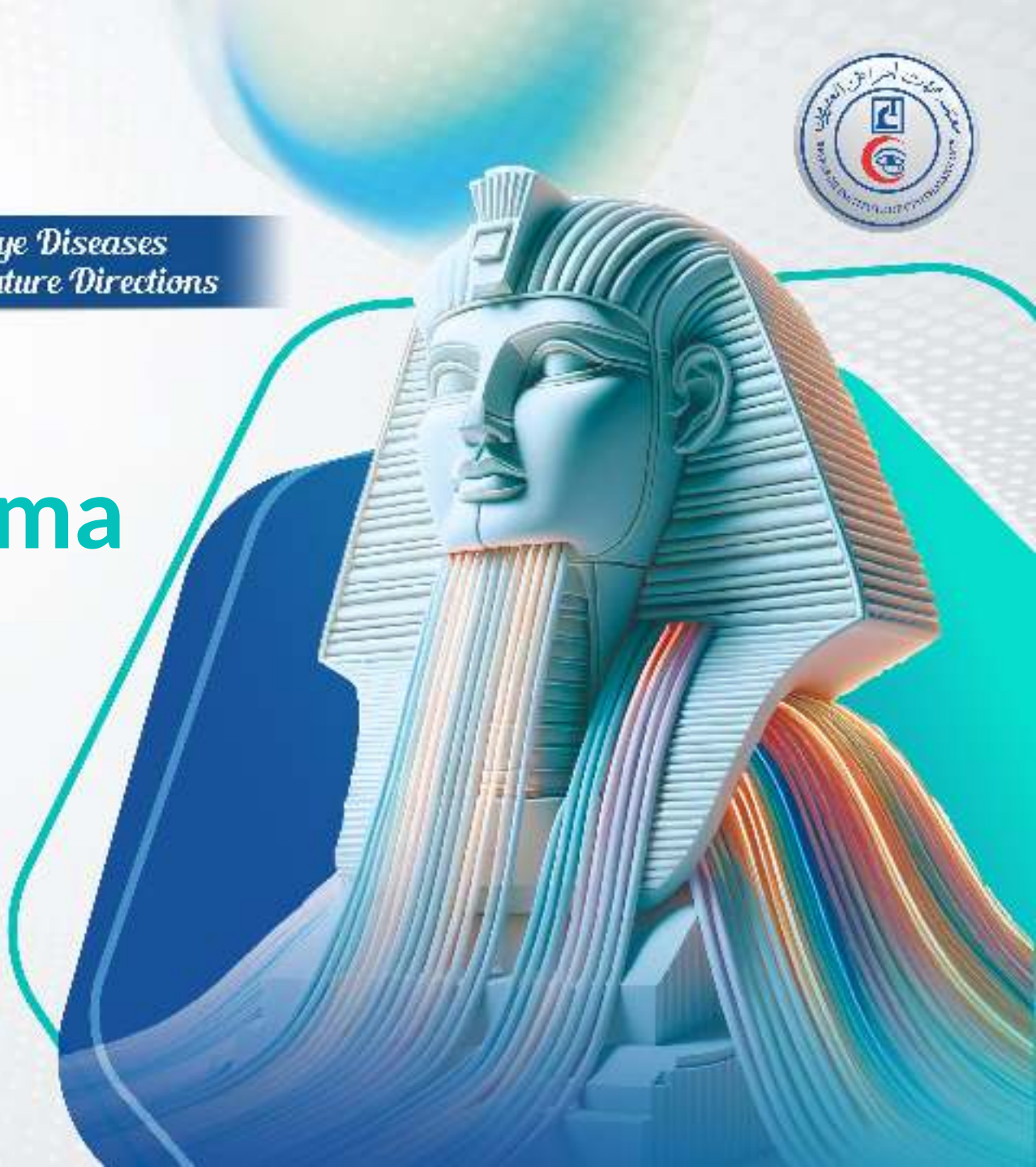
17TH INTERNATIONAL CONFERENCE OF THE RESEARCH INSTITUTE OF OPHTHALMOLOGY

RIO 2025

Anterior Segment Eye Diseases
Current Status & Future Directions

Personalising glaucoma care using genomics



Anthony Khawaja

Moorfields Eye Hospital

UCL Institute of Ophthalmology

Financial disclosures

- Consultant to Aerie, Allergan, Google Health, Novartis, Reichert, Santen, Thea
- Young Investigator Award from Alcon

Current management

Current evidence-based management

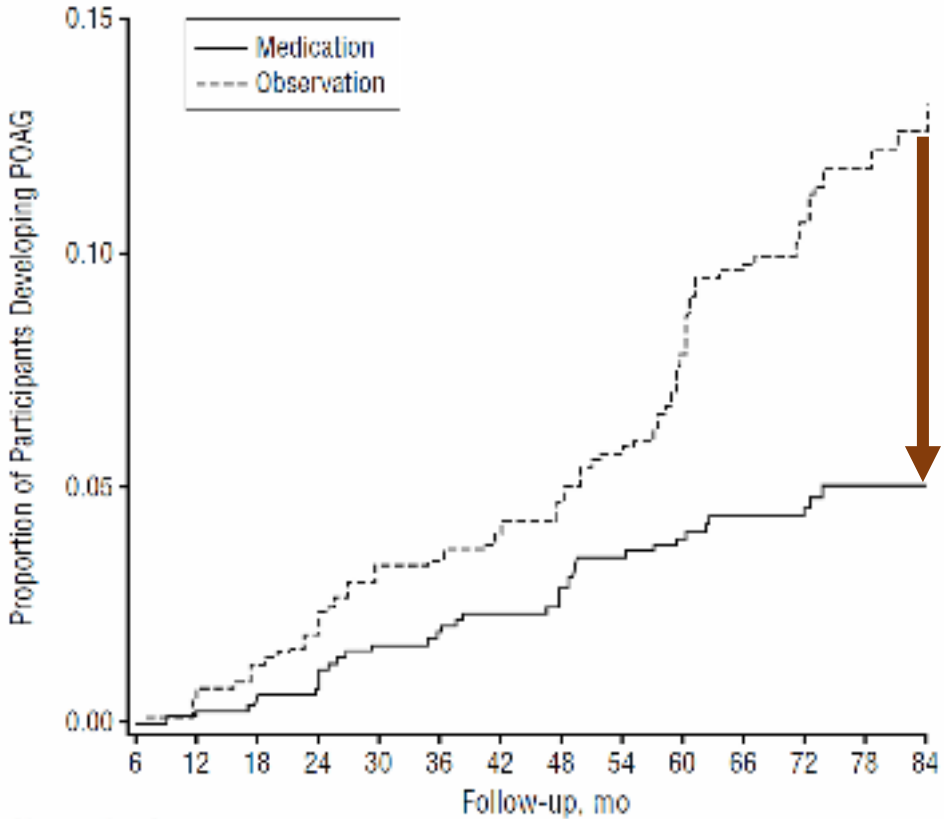
Current evidence-based management

CLINICAL SCIENCES

The Ocular Hypertension Treatment Study

ARCHIVES EXPRESS

A Randomized Trial Determines That Topical Ocular Hypotensive Medication Delays or Prevents the Onset of Primary Open-Angle Glaucoma

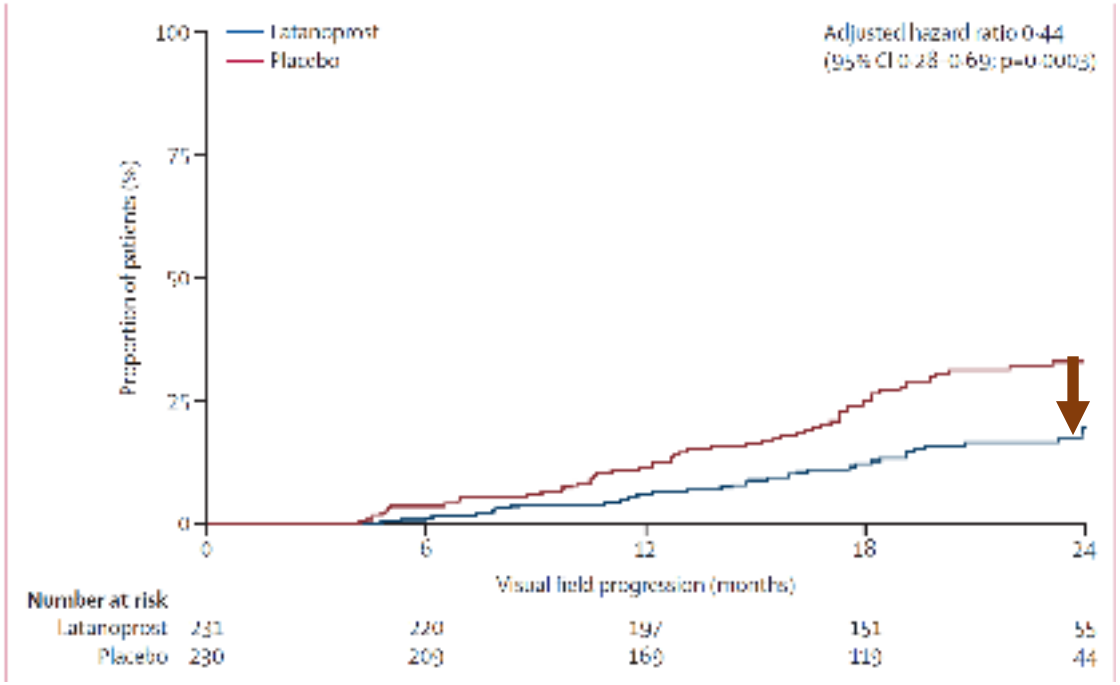


Only 12% of untreated converted to POAG

Kass MA, et al. Arch Ophthalmol. 2002;120:701–13

Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial

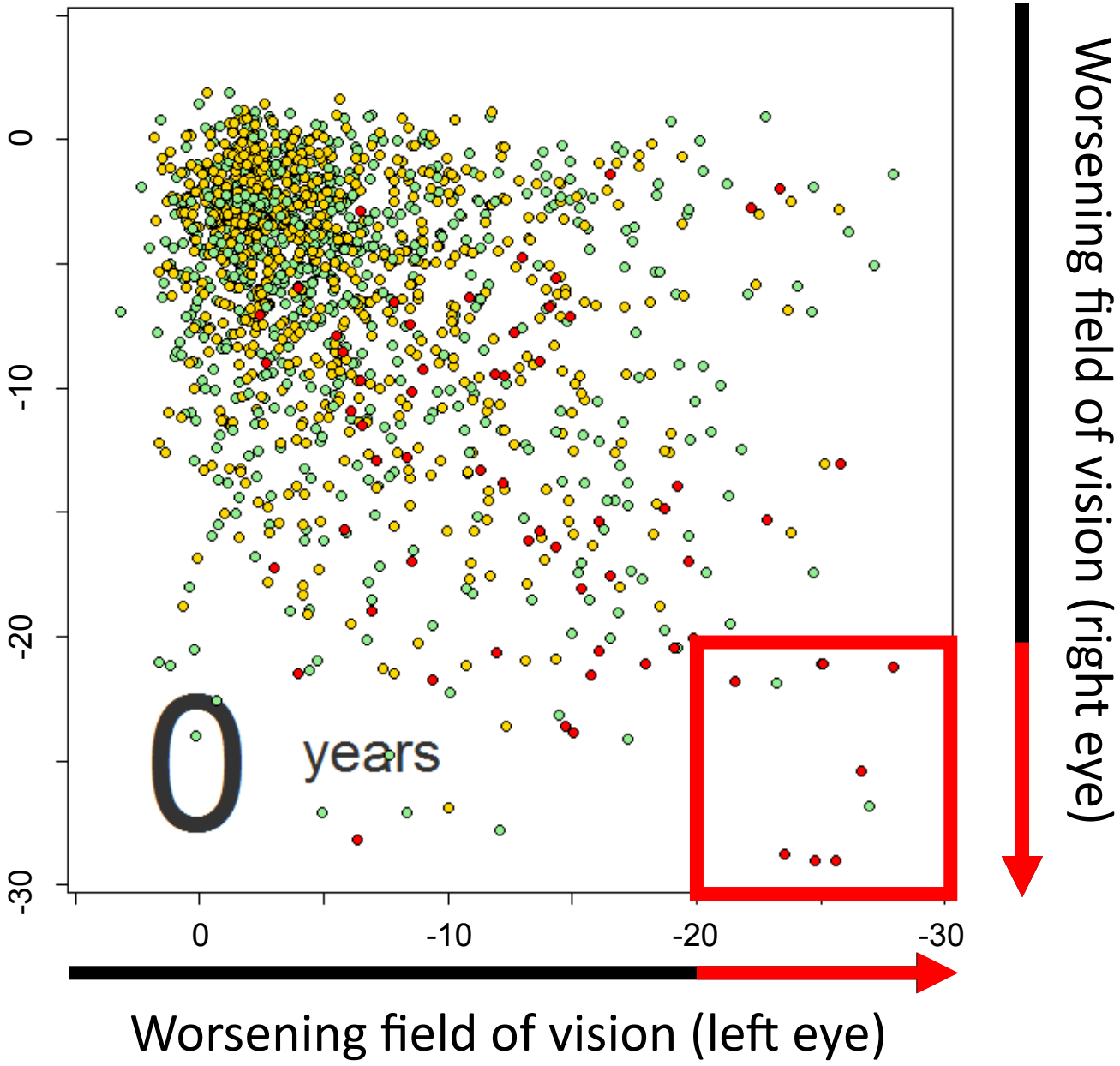
David F Garway-Heath, David P Crabb, Catey Bunce, Gerassimos Lascaratos, Francesca Amalfitano, Nitin Anand, Augusto Azuara-Blanco, Rupert R Bourne, David C Broadway, Ian A Cunliffe, Jeremy P Diamond, Scott G Fraser, Tuan A Ho, Keith R Martin, Andrew I McNaught, Anil Negi, Krishna Patel, Richard A Russell, Ameet Shah, Paul G Spry, Katsuyoshi Suzuki, Edward T White, Richard P Wormald, Wen Xing, Thierry G Zeyen



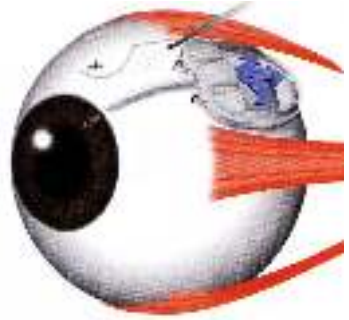
75% of placebo group did not progress

15% of treated group progressed

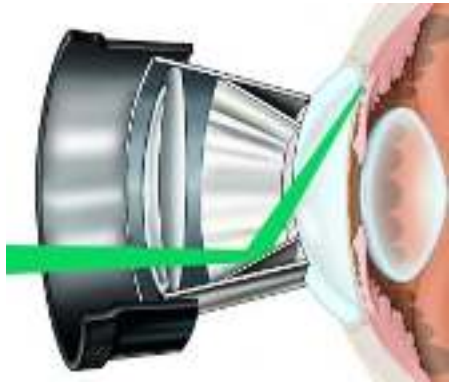
Garway-Heath DF, et al. Lancet 2015; 385:1295-304.



Saunders et al, PMID: 24282228



Which treatment?

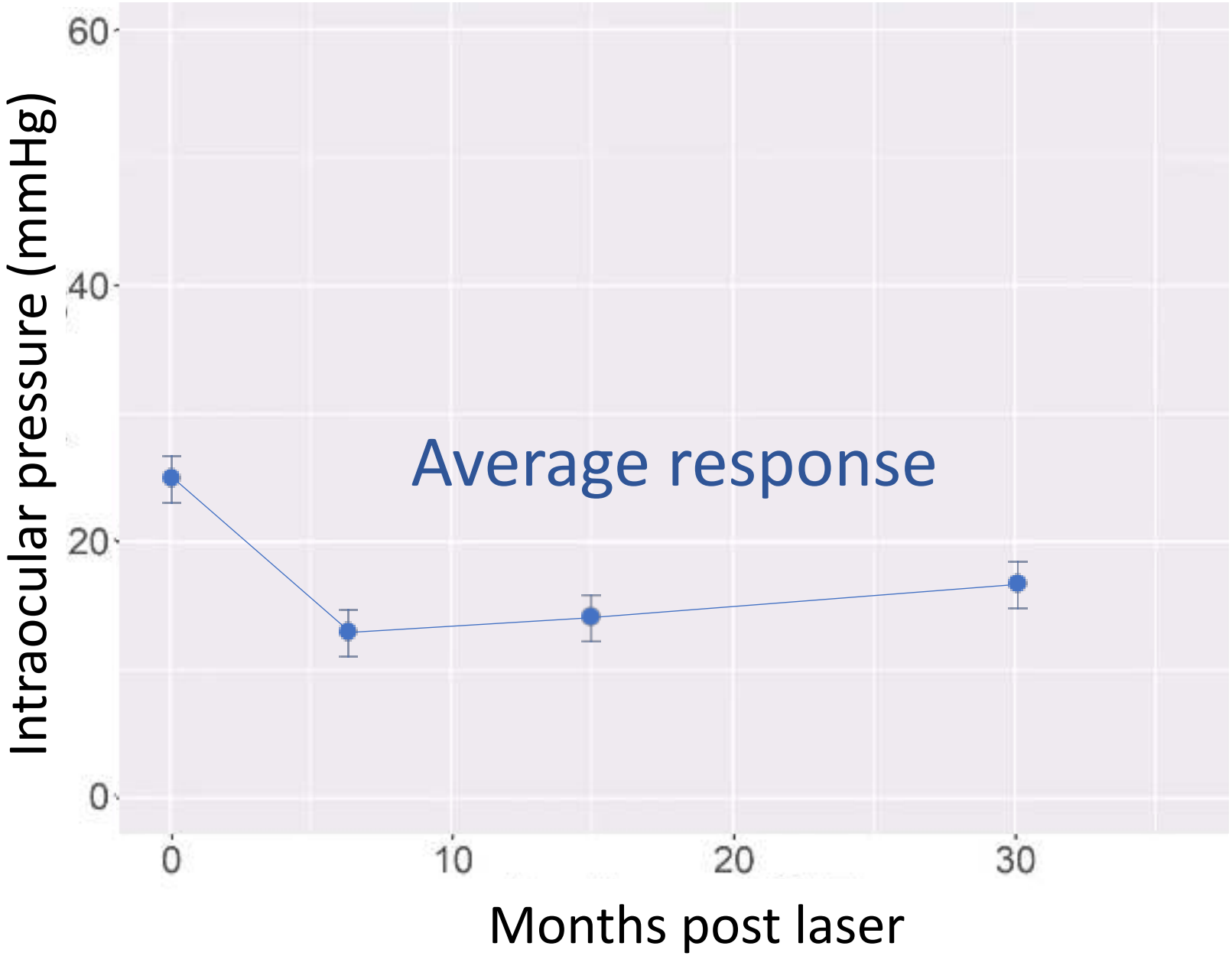


Selective laser trabeculoplasty versus eye drops for first-line treatment of ocular hypertension and glaucoma (LiGHT): a multicentre randomised controlled trial

*Gus Gazzard, Evgenia Konstantakopoulou, David Garway-Heath, Anurag Garg, Victoria Vickerstaff, Rachael Hunter, Gareth Ambler, Catey Bunce, Richard Wormald, Neil Nathwani, Keith Barton, Gary Rubin, Marta Buszewicz; on behalf of the LiGHT Trial Study Group**

74% drop-free at 3 years

Gazzard *et al. Lancet (London, England)* **6736**, 1–12 (2019)



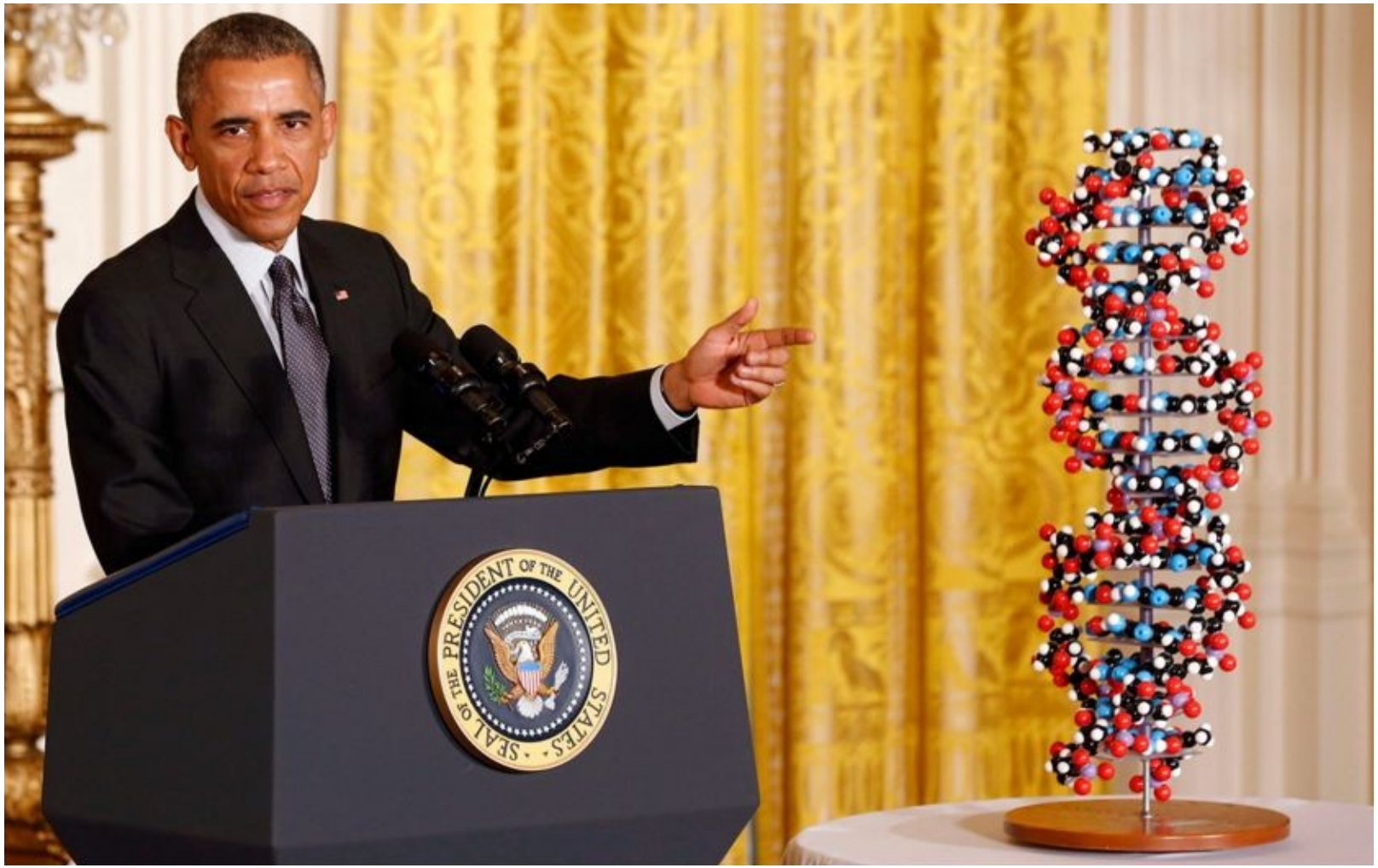
Khawaja *et al. Ophthalmology* **127**, 748–757

One size doesn’t fit all!

=

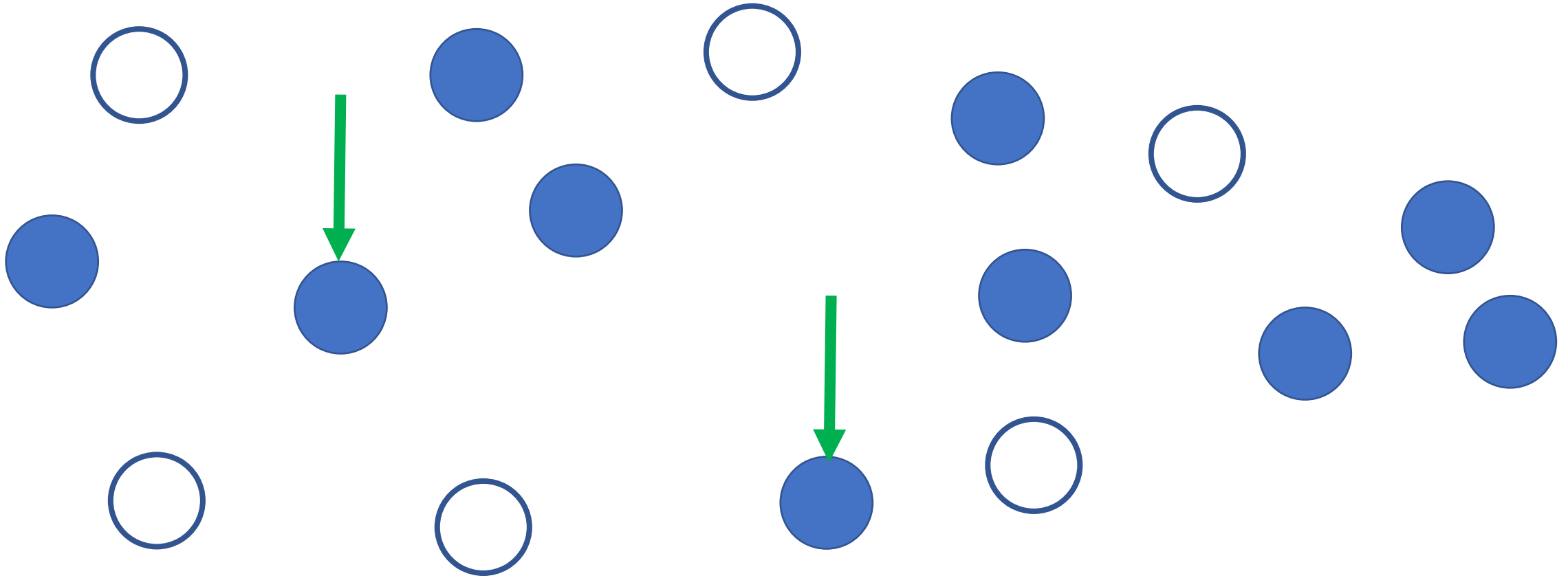
What's best ***on average***?

Precision Medicine Initiative (2015)



‘Simple’ versus ‘complex’ POAG

‘Simple’ POAG

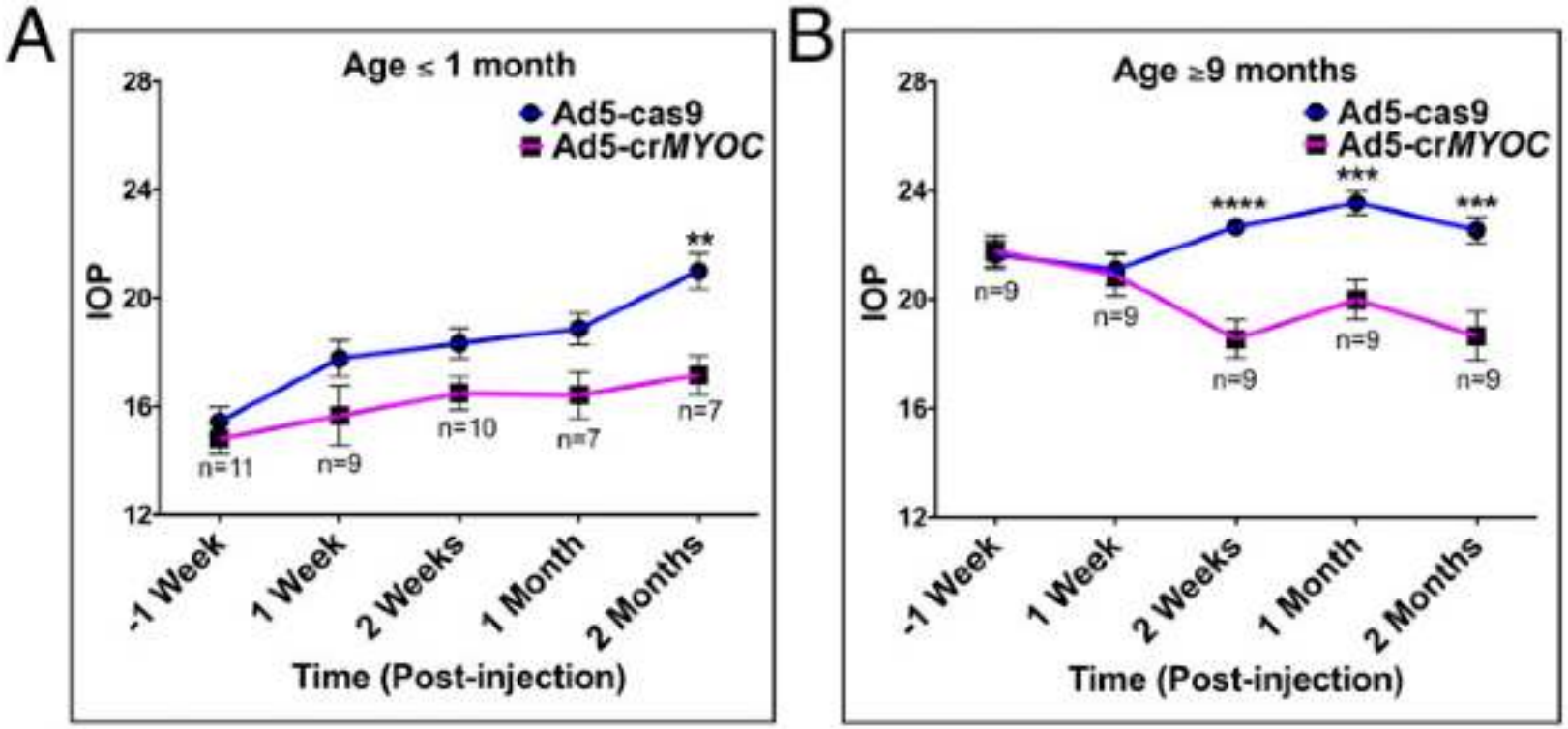


CRISPR-Cas9–based treatment of myocilin-associated glaucoma

Ankur Jain[a], Gulab Zode[b,1], Ramesh B. Kasetti[b], Fei A. Ran[c], Winston Yan[c], Tasneem P. Sharma[d], Kevin Bugge[a], Charles C. Searby[a], John H. Fingert[d], Feng Zhang[c], Abbot F. Clark[b], and Val C. Sheffield[a,d,1]

[a]Department of Pediatrics, Carver College of Medicine, University of Iowa, Iowa City, IA 52242; [b]North Texas Eye Research Institute, University of North Texas Health Science Center, Fort Worth, TX 76107; [c]McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, MA 02142; and [d]Stephen A. Wynn Institute for Vision Research, Department of Ophthalmology, Carver College of Medicine, University of Iowa, Iowa City, IA 52242

PNAS | October 17, 2017 | vol. 114 | no. 42 | 11199–11204



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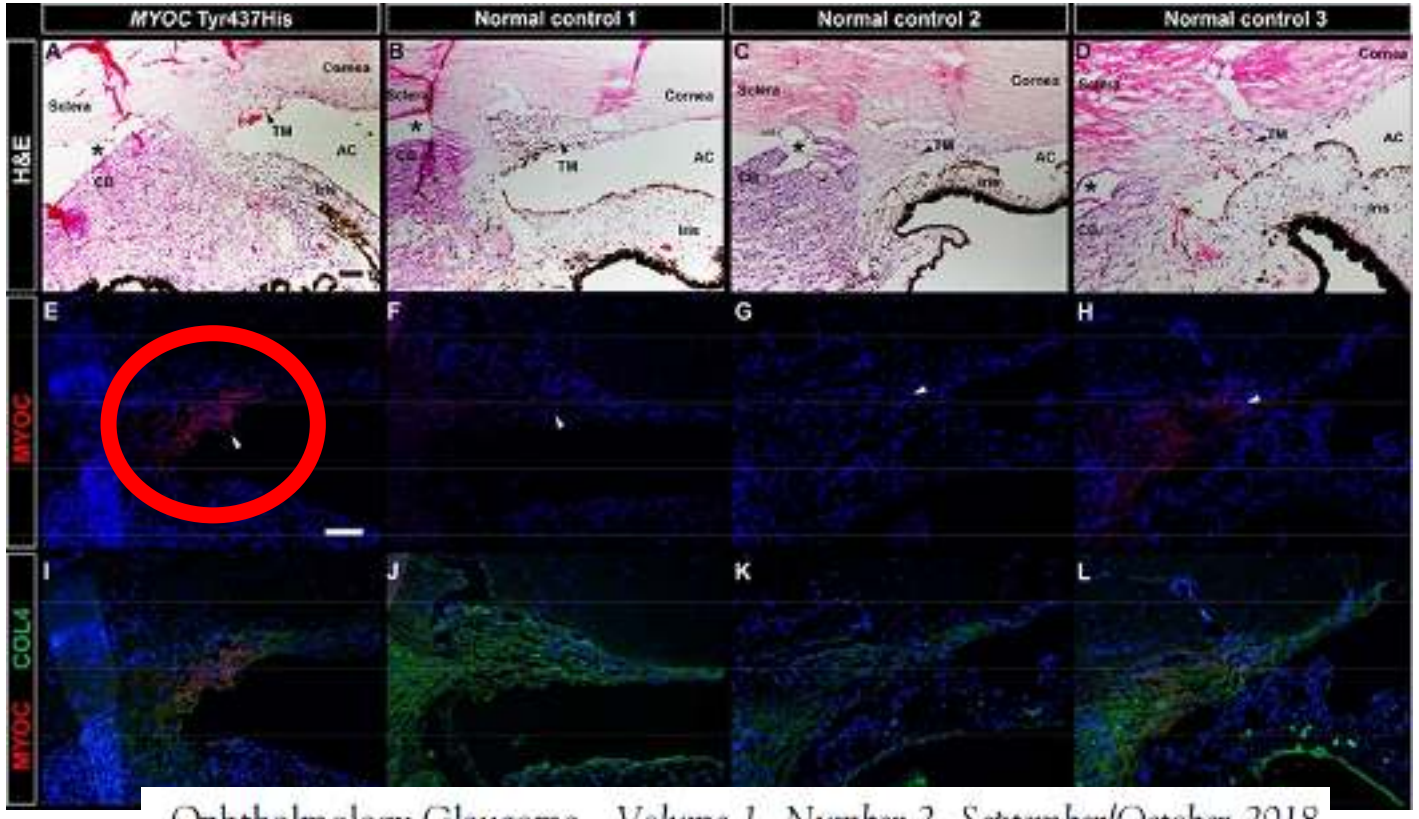
In partnership with the AMERICAN GLAUCOMA SOCIETY

Histochemical Analysis of Glaucoma Caused by a Myocilin Mutation in a Human Donor Eye

Carly J. van der Heide, BS,[1,2,3] Wallace L.M. Alward, MD,[1,2] Miles Flamme-Wiese, BSE,[1,2] Megan Riker, BS,[1,2] Nasreen A. Syed, MD,[1,4] Michael G. Anderson, PhD,[1,2,3,5] Keith Carter, MD, FACS,[1] Markus H. Kuehn, PhD,[1,2] Edwin M. Stone, MD, PhD,[1,2] Robert F. Mullins, PhD,[1,2] John H. Fingert, MD, PhD[1,2]



Ophthalmology Glaucoma *Volume 1, Number 2, September/October 2018*

AMERICAN ACADEMY OF OPHTHALMOLOGY®

In partnership with the AMERICAN GLAUCOMA SOCIETY

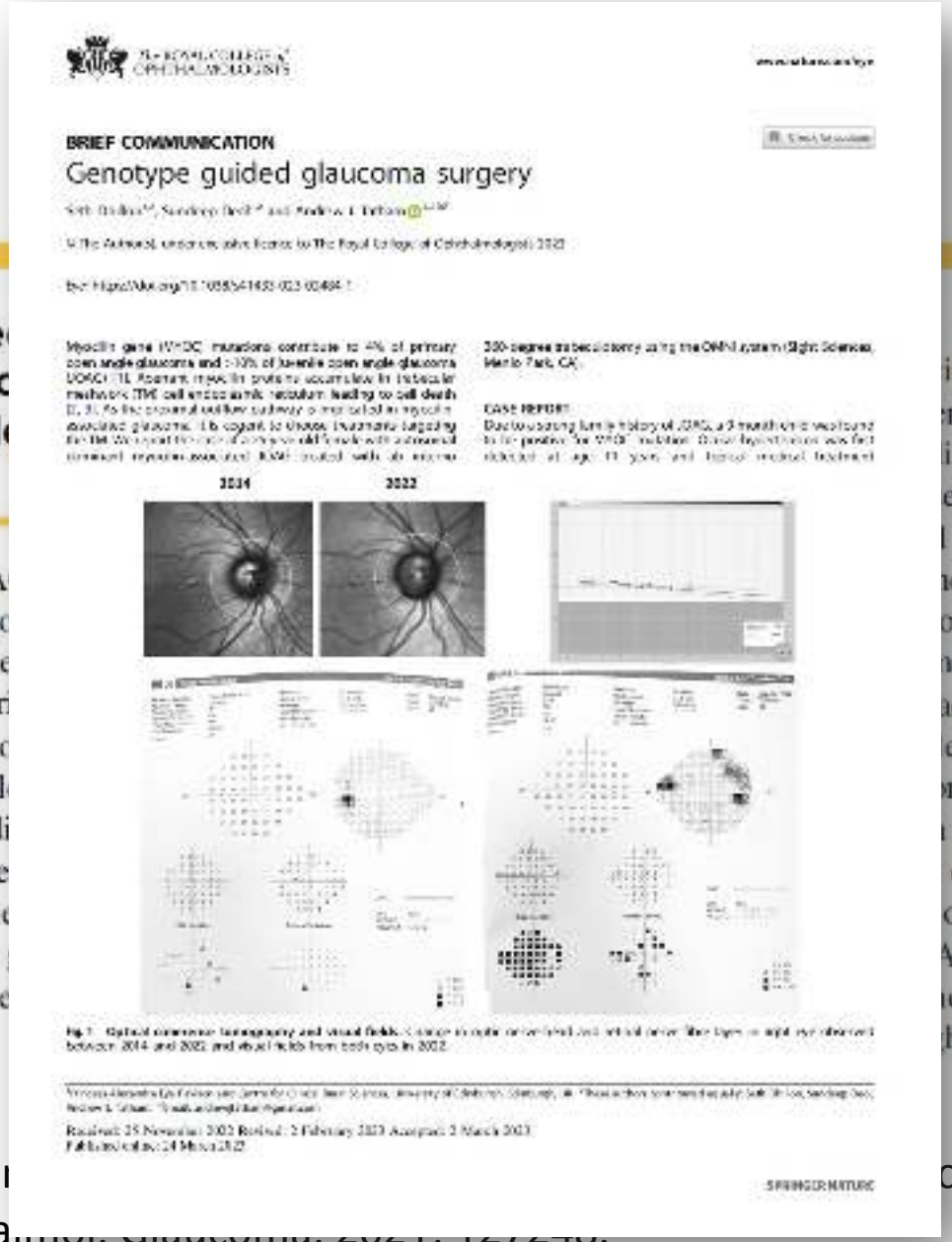
Gonioscopy-Assiste… Transluminal Trabec… for Myocilin Juvenil… Glaucoma

Juvenile open-angle glaucoma (JOA… glaucoma and occurs in patients y… tions in the myocilin (*MYOC*) gene… simple genetic causes of both pr… (POAG) and JOAG.[1,2] *MYOC*-asso… young age, produces markedly el… (IOPs), and is often resistant to medi…

Myocilin encodes a glycoprote… trabecular meshwork (TM) into the… *MYOC* protein encoded by a mutant … within TM cells and ultimately cause… outflow, high IOP, and glaucoma.[4]

…visual fields (Zeiss) (Fig 1B). …ines (brimonidine, dorzolamide, …ered her IOP to 14 mmHg. …iscontinued because of drop …ed to the low 20s (mmHg). At …l to 34 mmHg in the right eye …d brimonidine was added again …ontrol. When she was 17 years …mHg in the right eye and 45 …addition of oral acetazolamide …erable because of fatigue. After …r 2 weeks, she and her family …eyes.

…options, reduce the risk of com- …of life, we treated our patient's …ATT. With the use of the iTrack …c.), she underwent an uncompli- …ht eye in January 2020, followed



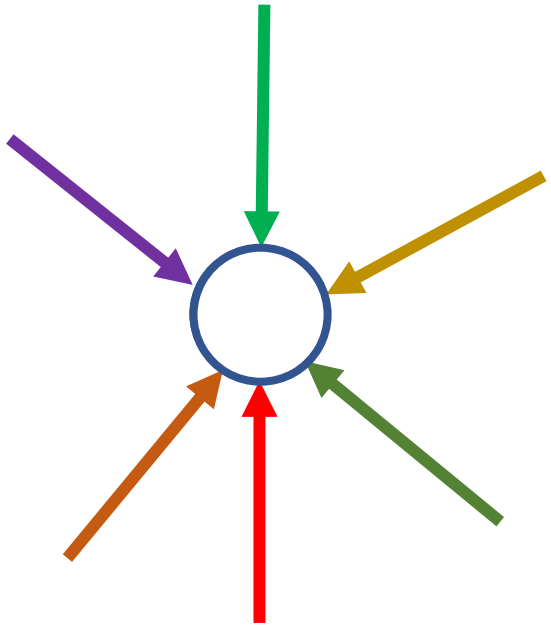
BRIEF COMMUNICATION

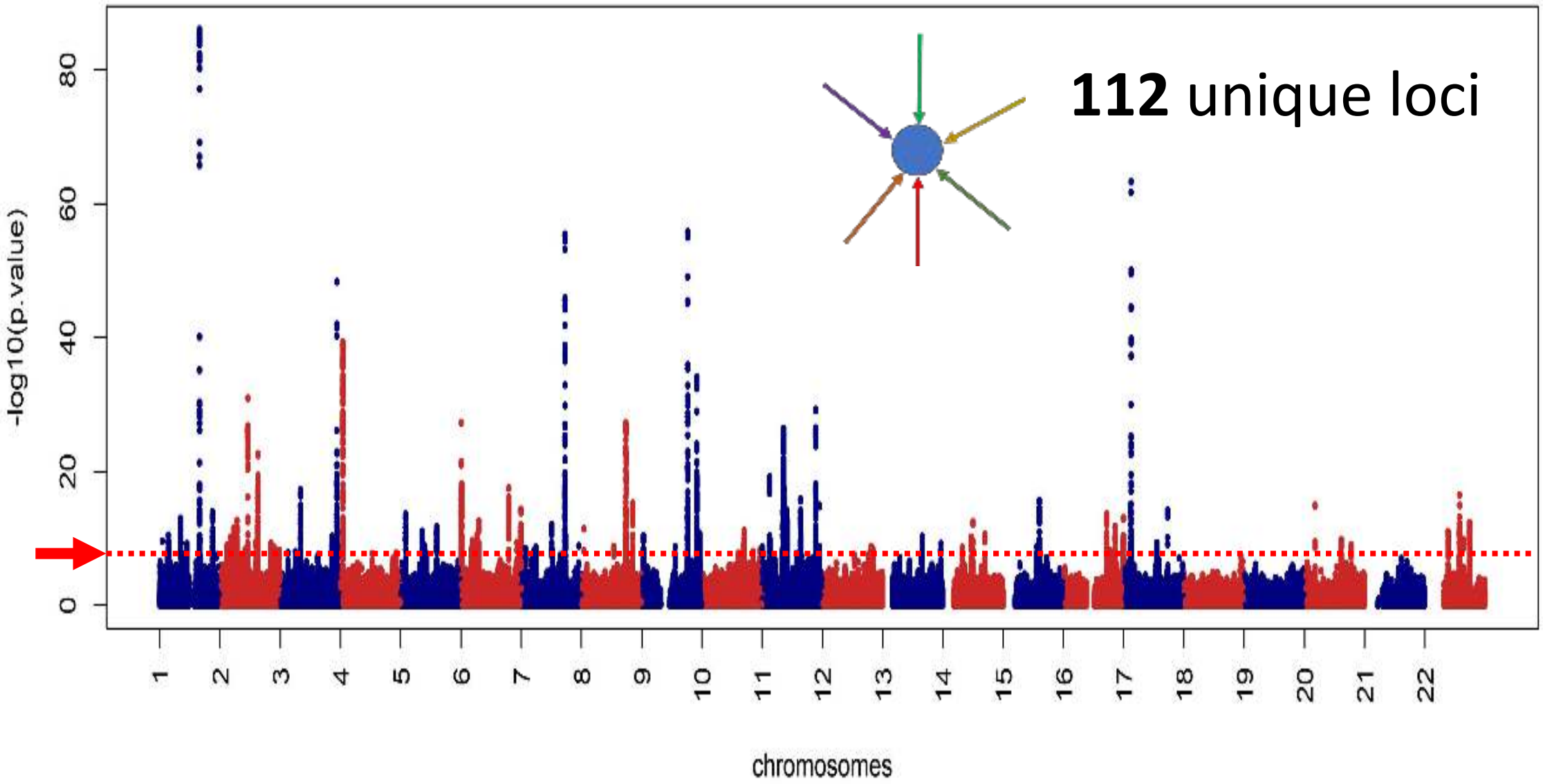
Genotype guided glaucoma surgery

2014 2022

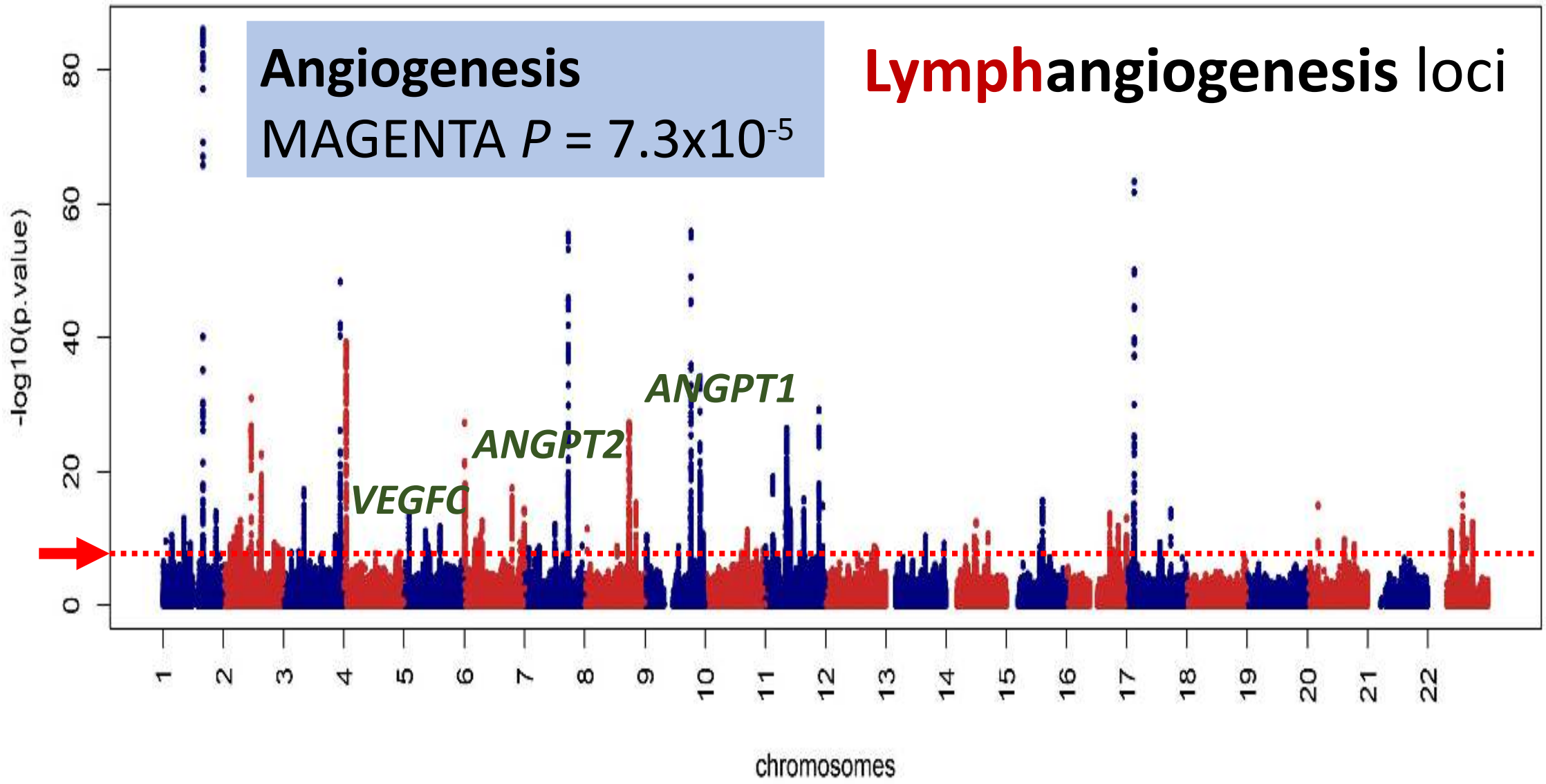
Boese EA, Alward WLM, Fi… …culotomy (GATT) for myocilin juvenile glaucoma. Ophtha…mol. Glaucoma. 2021; 12:243.

‘Complex’ POAG





Khawaja et al, Nature Genetic 2018

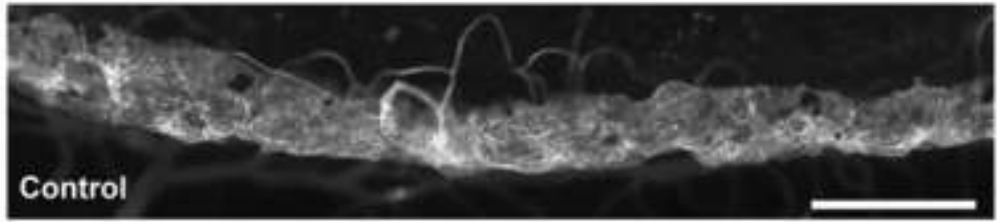


Khawaja et al, Nature Genetic 2018

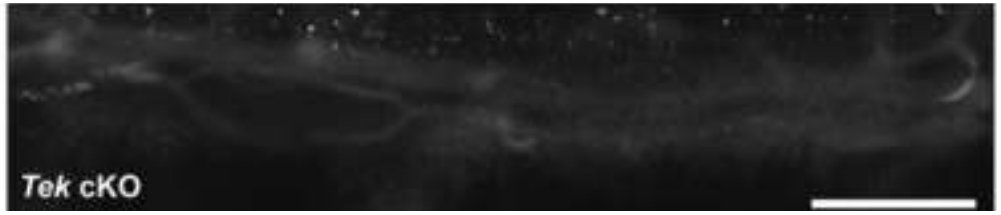
The Journal of Clinical Investigation RESEARCH ARTICLE

Angiopoietin receptor TEK mutations underlie primary congenital glaucoma with variable expressivity

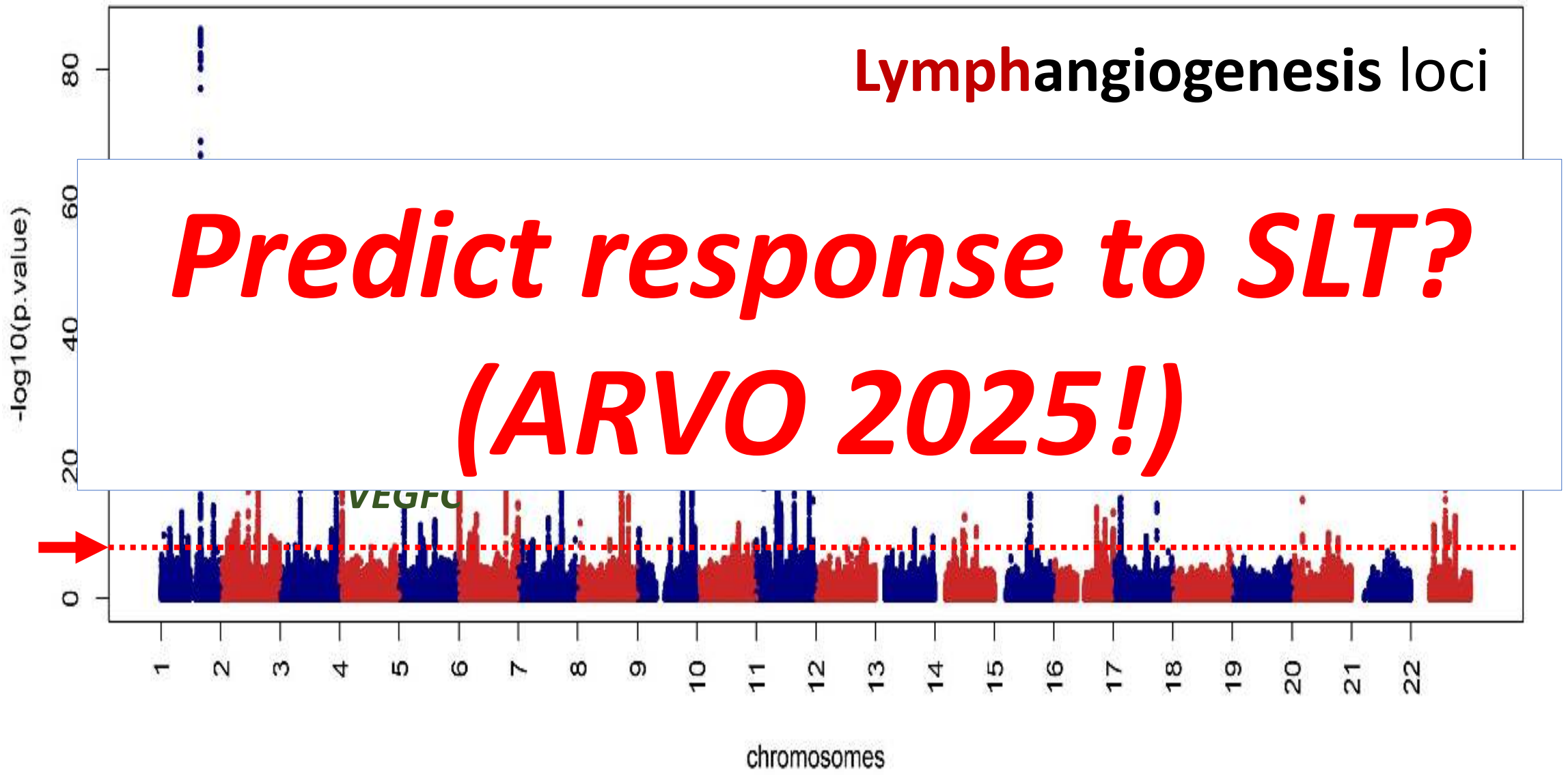
Tomokazu Souma,[1,2] Stuart W. Tompson,[3] Benjamin R. Thomson,[1,2] Owen M. Siggs,[4] Krishnakumar Kizhatil,[5] Shinji Yamaguchi,[1,2] Liang Feng,[6] Vachiranee Limviphuvadh,[7] Kristina N. Whisenhunt,[3] Sebastian Maurer-Stroh,[7,8] Tammy L. Yanovitch,[3] Luba Kalaydjieva,[10] Dimitar N. Azmanov,[10,11] Simone Finzi,[12] Lucia Mauri,[13] Shahrbanou Javadiyan,[4] Emmanuelle Souzeau,[4] Tiger Zhou,[4] Alex W. Hewitt,[14,15,16] Bethany Kloss,[3] Kathryn P. Burdon,[4,16] David A. Mackey,[15,16] Keri F. Allen,[17] Jonathan B. Ruddle,[14] Sing-Hui Lim,[18] Steve Rozen,[18] Khanh-Nhat Tran-Viet,[19] Xiaorong Liu,[6] Simon John,[5,20] Janey L. Wiggs,[17] Francesca Pasutto,[21] Jamie E. Craig,[4] Jing Jin,[1,2] Susan E. Quaggin,[1,2] and Terri L. Young[3,18]



Control



Absent Schlemm's canal, normal TM


Lymphangiogenesis loci
Predict response to SLT?
(ARVO 2025!)
-log10(p.value)
0
20
40
60
80
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
chromosomes

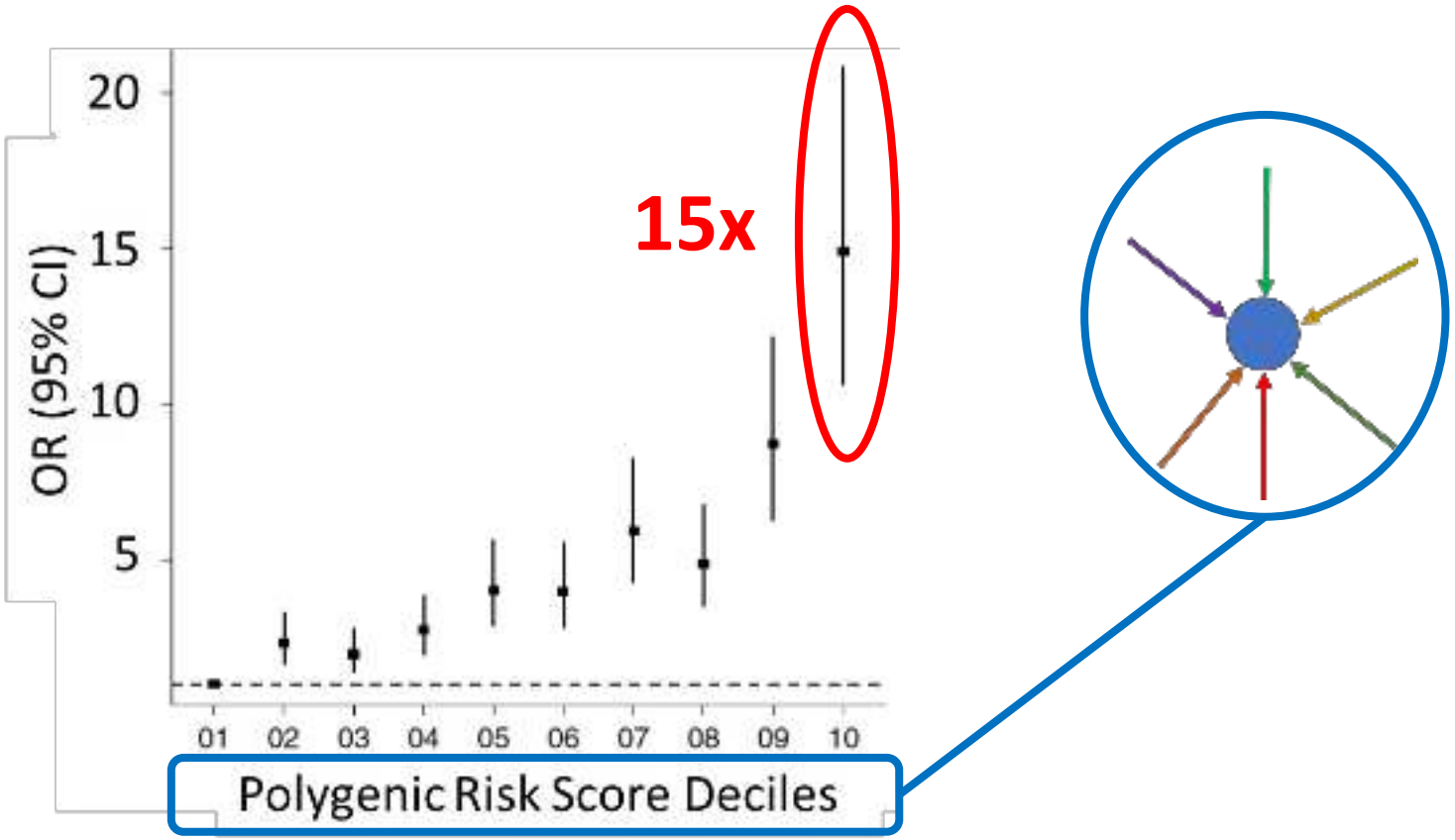
nature genetics

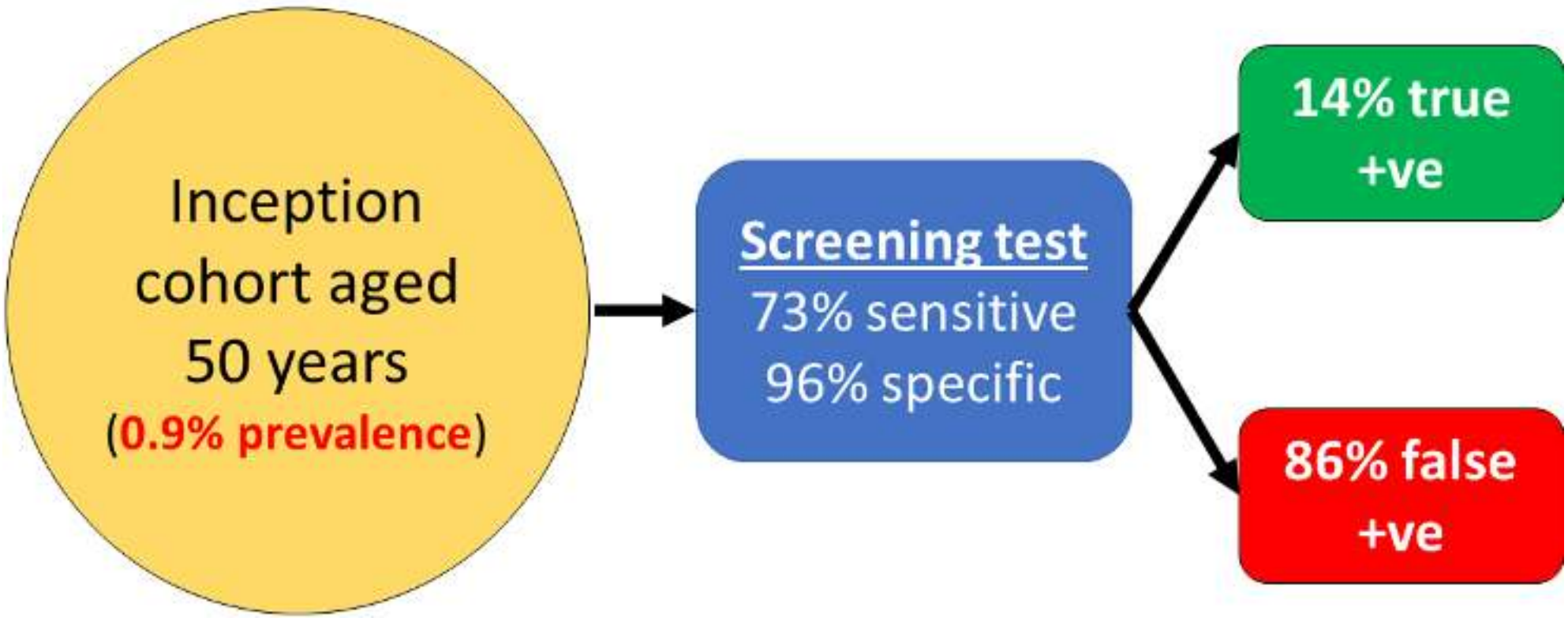
ARTICLES

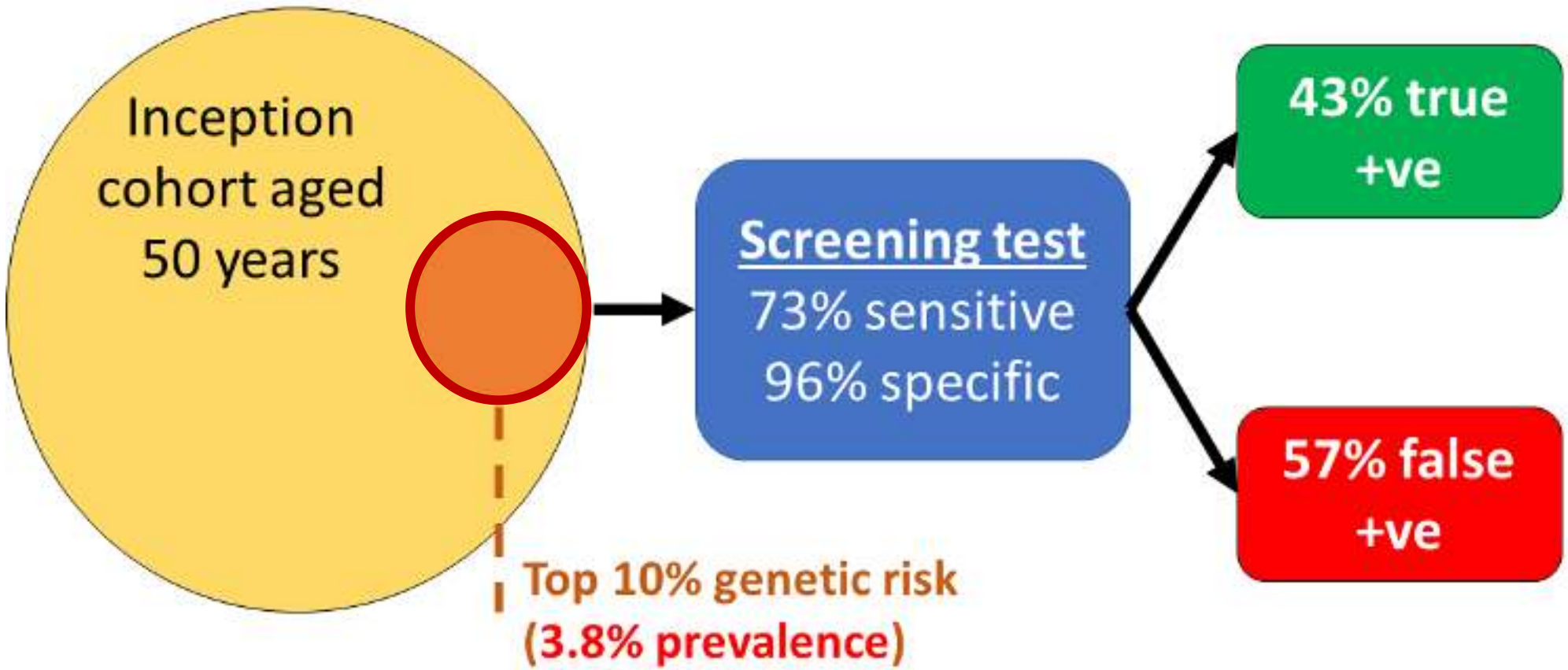
https://doi.org/10.1038/s41588-019-0556-y

Multitrait analysis of glaucoma identifies new risk loci and enables polygenic prediction of disease susceptibility and progression

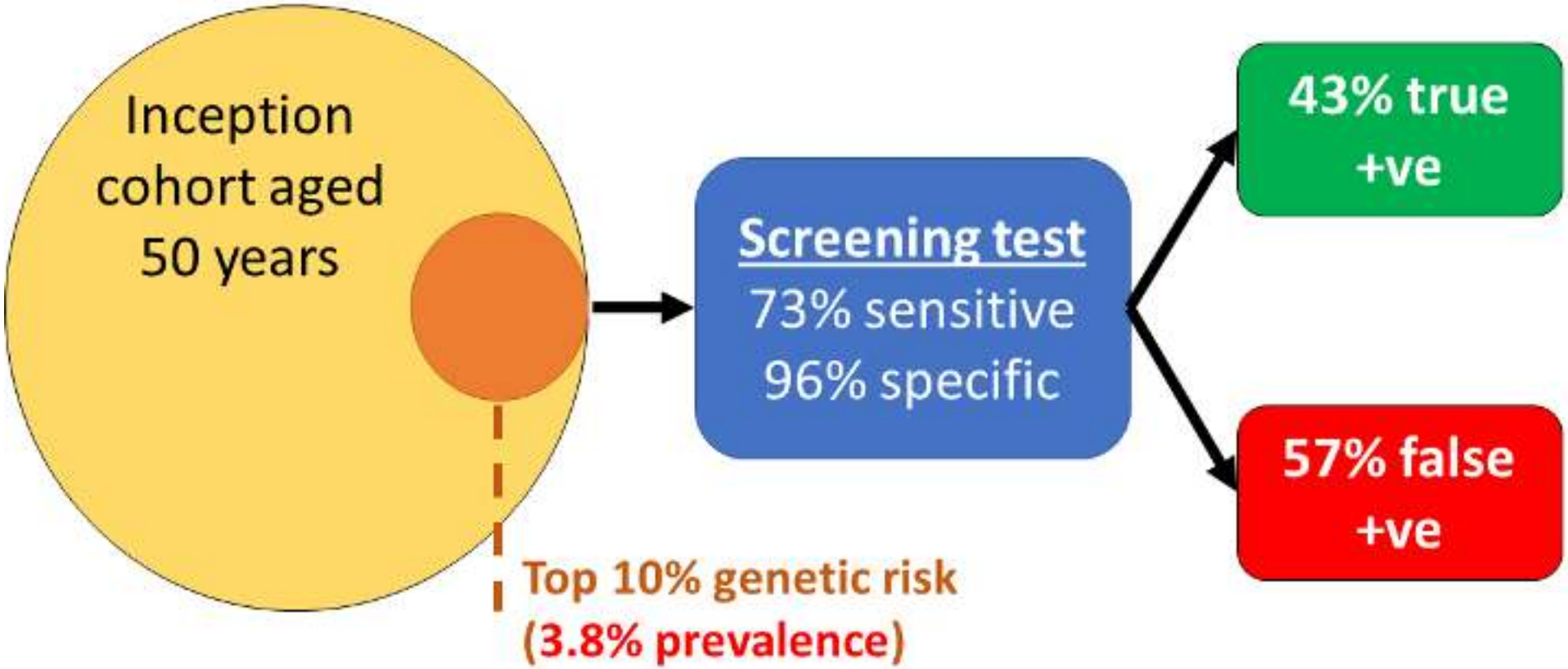
Jamie E. Craig[1,40], Xikun Han[2,3,40*], Ayub Qassim[1,40], Mark Hassall[1], Jessica N. Cooke Bailey[4], Tyler G. Kinzy[4], Anthony P. Khawaja[5], Jiyuan An[2], Henry Marshall[1], Puya Gharahkhani[2],




Inception cohort aged 50 years
(0.9% prevalence)
Screening test
73% sensitive
96% specific
14% true +ve
86% false +ve


Inception cohort aged 50 years
Top 10% genetic risk (3.8% prevalence)
Screening test
73% sensitive
96% specific
43% true +ve
57% false +ve

Personalised population screening



EGS Screening Task Force

WG1: GENOMICS ENABLING TARGETED SCREENING

Nomdo Jansonius, Anthony Khawaja


WG2: AI-IMAGING TECHNOLOGIES FOR SCREENING

Luis Pinto, Alex Schuster, Ingeborg Stalmans, Marta Pazos, Hans Lemij

WG3: GLAUCOMA NATURAL HISTORY (Clinic-based studies)

Frances Meier-Gibbons, Panayiota Founti, Esther Hoffman, Dimitris Giannoulis

WG4: MODELLING OF POTENTIAL SCREENING PROGRAMMES

Ananth Viswanathan, Ted Garway-Heath, Bart-Jan Boverhof

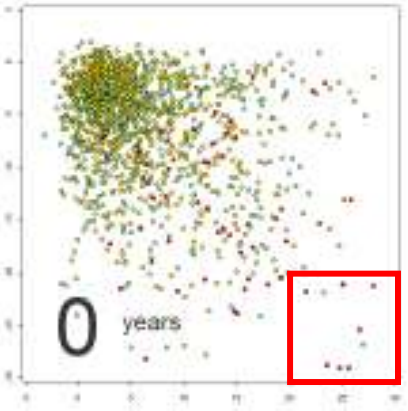
WG5: PUBLIC ACCEPTANCE AND ENGAGEMENT

Andrew Tatham, Andrew Scott, Sanna Leinonen, Anja Tuulonen, Gauti Johannesson

WG6: PROSPECTIVE RCT PLANNING

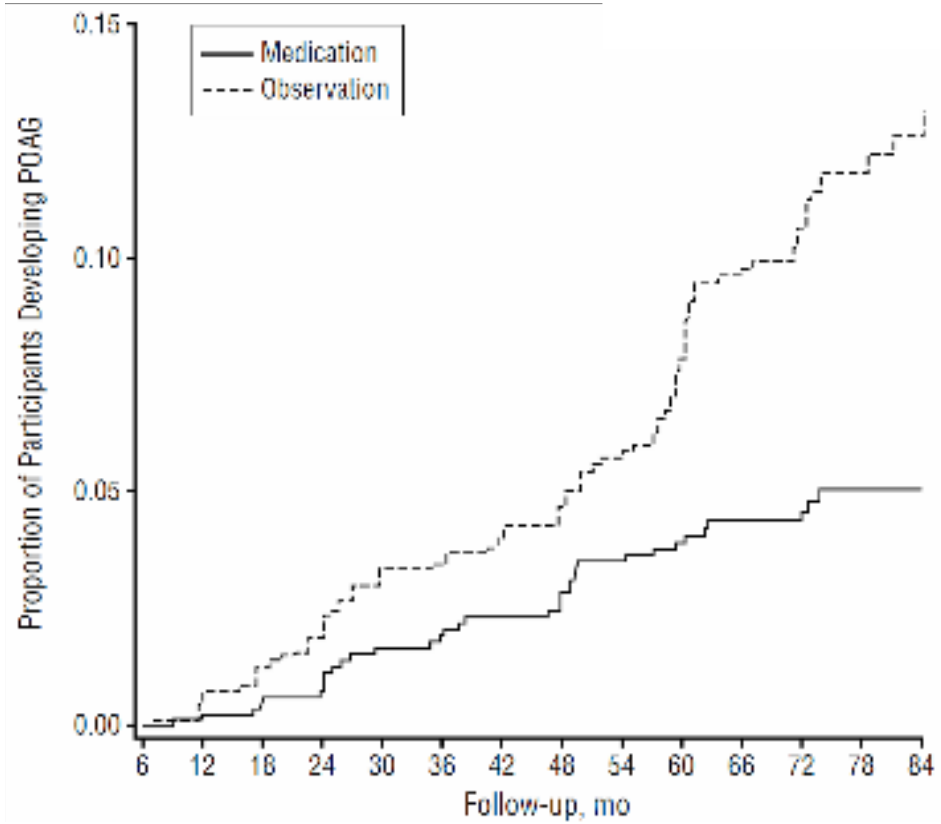
Anthony Khawaja, Augusto Azuara-Blanco, Jen Burr, Dimitris Giannoulis

Predicting disease prognosis

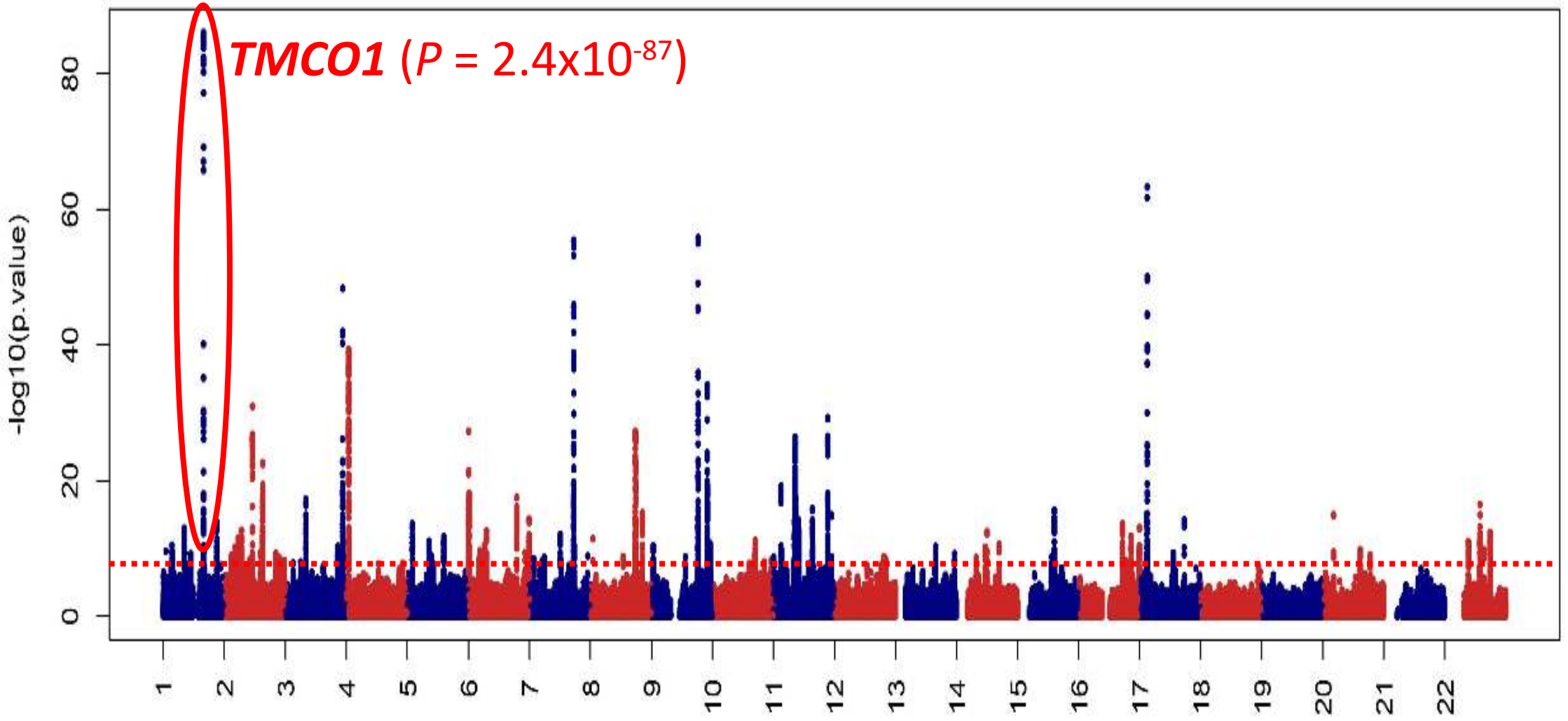


CLINICAL SCIENCES

The Ocular Hypertension Treatment Study



Ocular Hypertension Treatment Study Group 2007;114:10–19.e2.



Khawaja *et al*, Nature Genetics, 2018

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OF OPHTHALMOLOGY

Glaucoma Risk Alleles in the Ocular Hypertension Treatment Study

Todd E. Scheetz, PhD,[1,2] Ben Faga, BS,[1,2] Lizette Ortega, BS,[3] Ben R. Roos, BS,[1,2] Mae O. Gordon, PhD,[4] Michael A. Kass, MD,[4] Kai Wang, PhD,[2,3] John H. Fingert, MD, PhD[1,2]

Ophthalmology *Volume 123, Number 12, December 2016*

Scheetz TE, et al. Ophthalmol. 2016; 123:2527–2536.

	Hazard Ratio	95% Confidence Interval	*P* Value
Age (decade)	1.40	1.14–1.71	0.0011
Gender (male)	1.53	1.05–2.23	0.025
IOP (per 2.7 mmHg [SE])	1.28	1.03–1.46	0.021
CCT (per 37 μm [SE])	1.57	1.30–1.89	0.0000028
Vertical cup-to-disc ratio (per 0.19 [SE])	1.62	1.33–1.96	0.00000096
Visual Field defect (PSD, per 0.25 [SE])	1.20	0.99–1.45	0.070
TMCO1 (per risk allele)	1.73	1.28–2.34	0.00036

3-fold increased risk (for 2 risk alleles)

Equivalent to **33 years older**!

or **0.43 larger CDR**!

or **12 mmHg higher IOP**!

Scheetz TE, et al. Ophthalmol. 2016; 123:2527–2536.

Research

JAMA Ophthalmol. doi:10.1001/jamaophthalmol.2024.4376
Published online November 7, 2024.

JAMA Ophthalmology | **Original Investigation**

Primary Open-Angle Glaucoma Polygenic Risk Score and Risk of Disease Onset

A Post Hoc Analysis of a Randomized Clinical Trial

Sayuri Sekimitsu, MD; Nabil Ghazal, BS; Kanza Aziz, MB, BS; Yan Zhao, MS; Rishabh K. Singh, MD; John H. Fingert, MD, PhD; Mae O. Gordon, PhD; Michael A. Kass, MD; Todd Scheetz, MS, PhD; Ayellet V. Segrè, PhD; Louis R. Pasquale, MD; Janey L. Wiggs, MD, PhD; James D. Brandt, MD; Nazlee Zebardast, MD, MS

Research

JAMA Ophthalmol. doi:10.1001/jamaophthalmol.2024.4376
Published online November 7, 2024.

JAMA Ophthalmology | Original Investigation

Primary Open-Angle Glaucoma Polygenic Risk Score and Risk of Disease Onset

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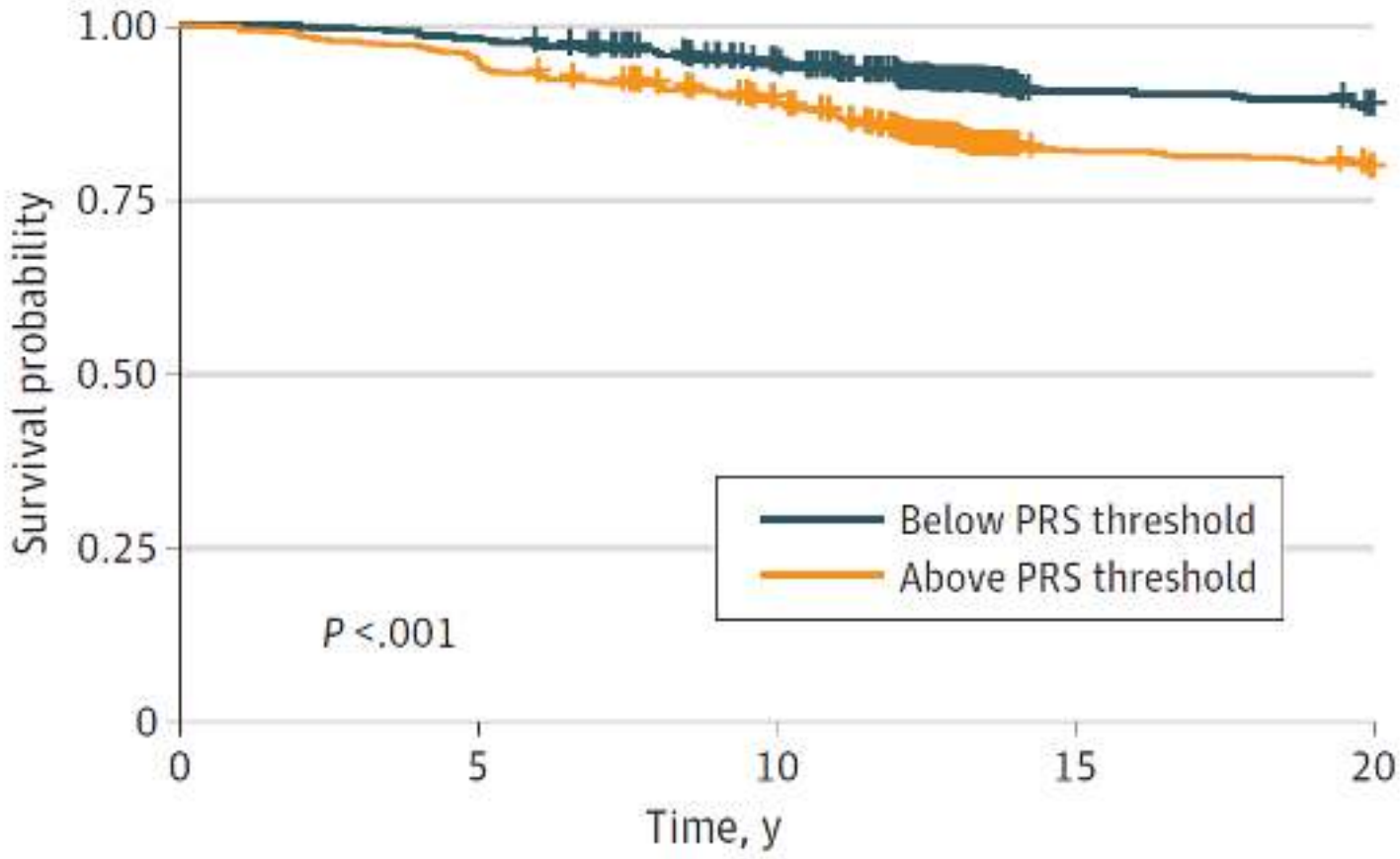
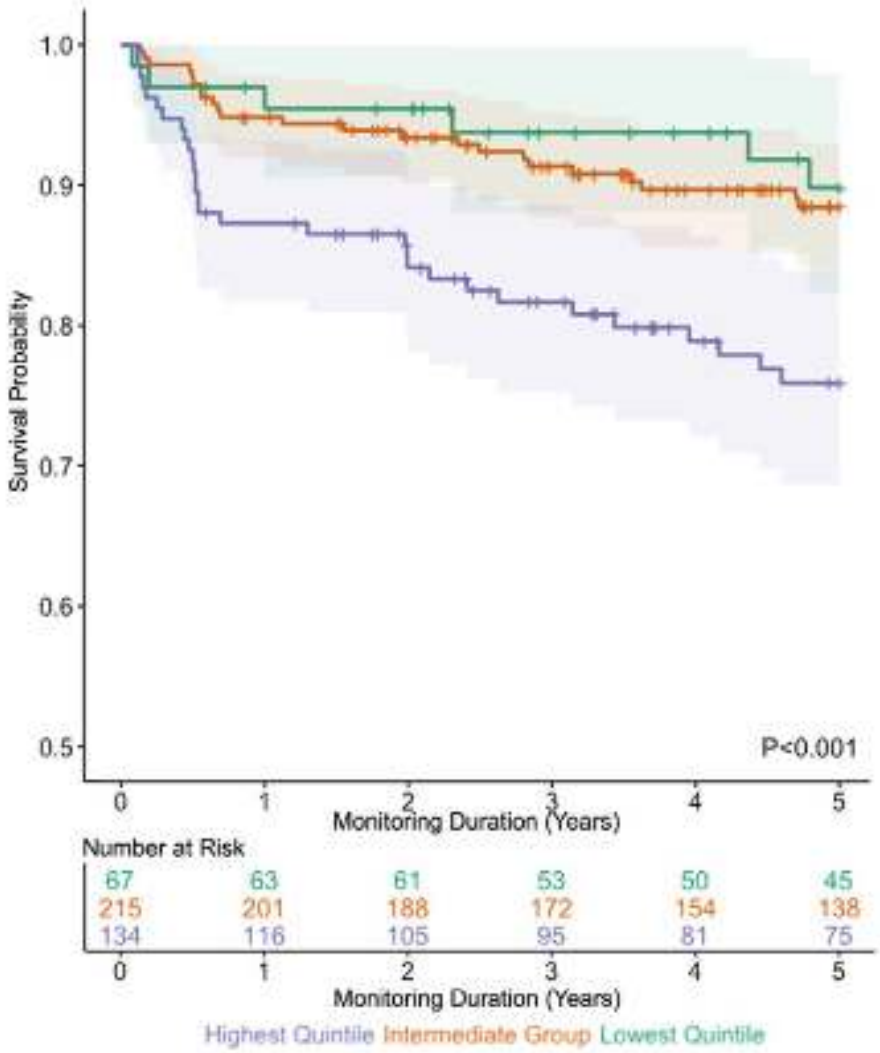
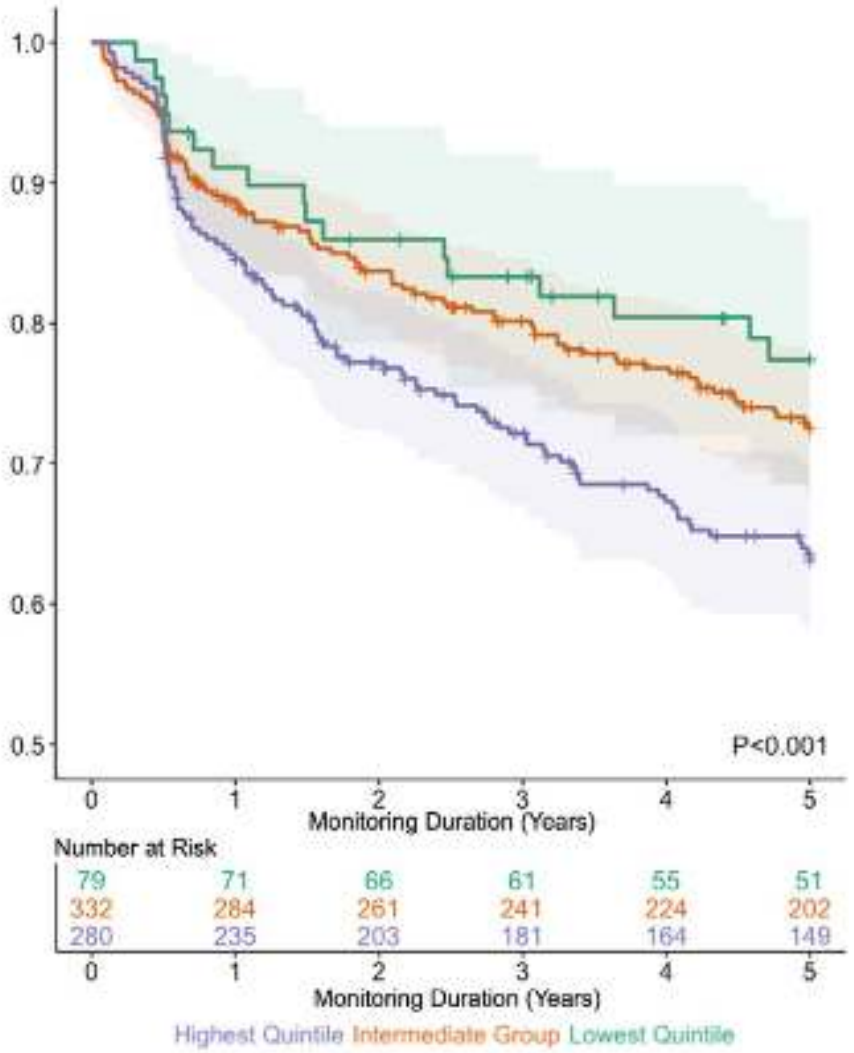


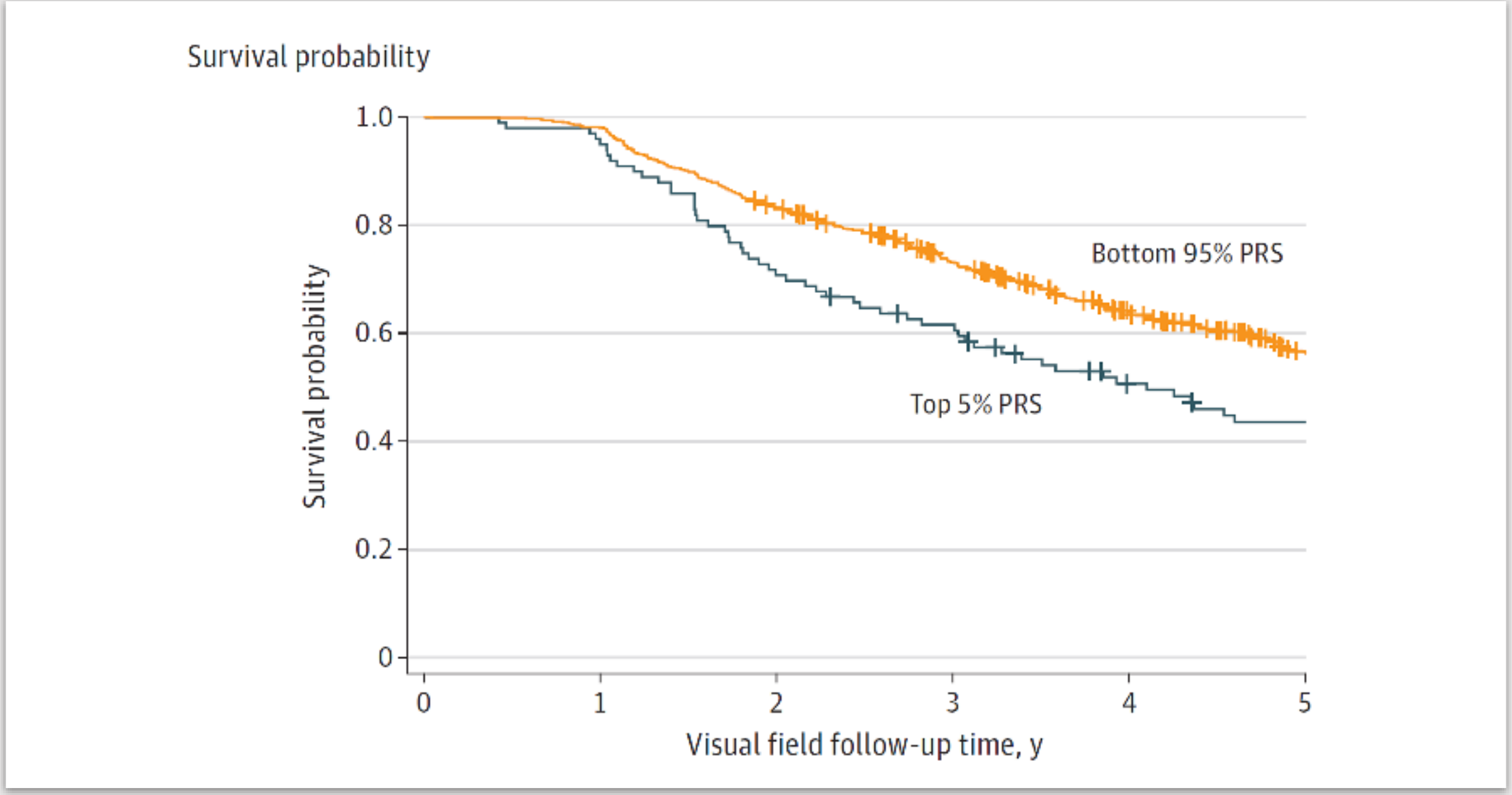
Rx commencement



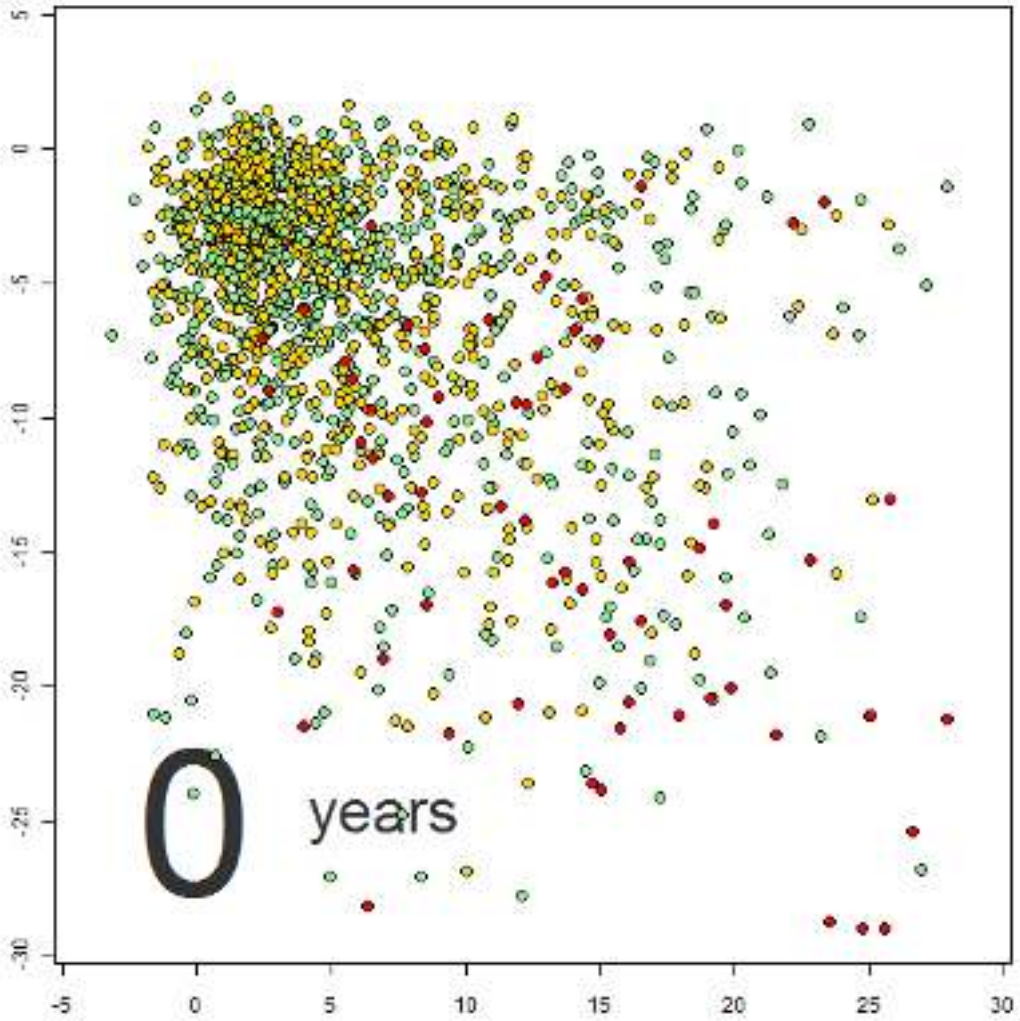
Rx escalation

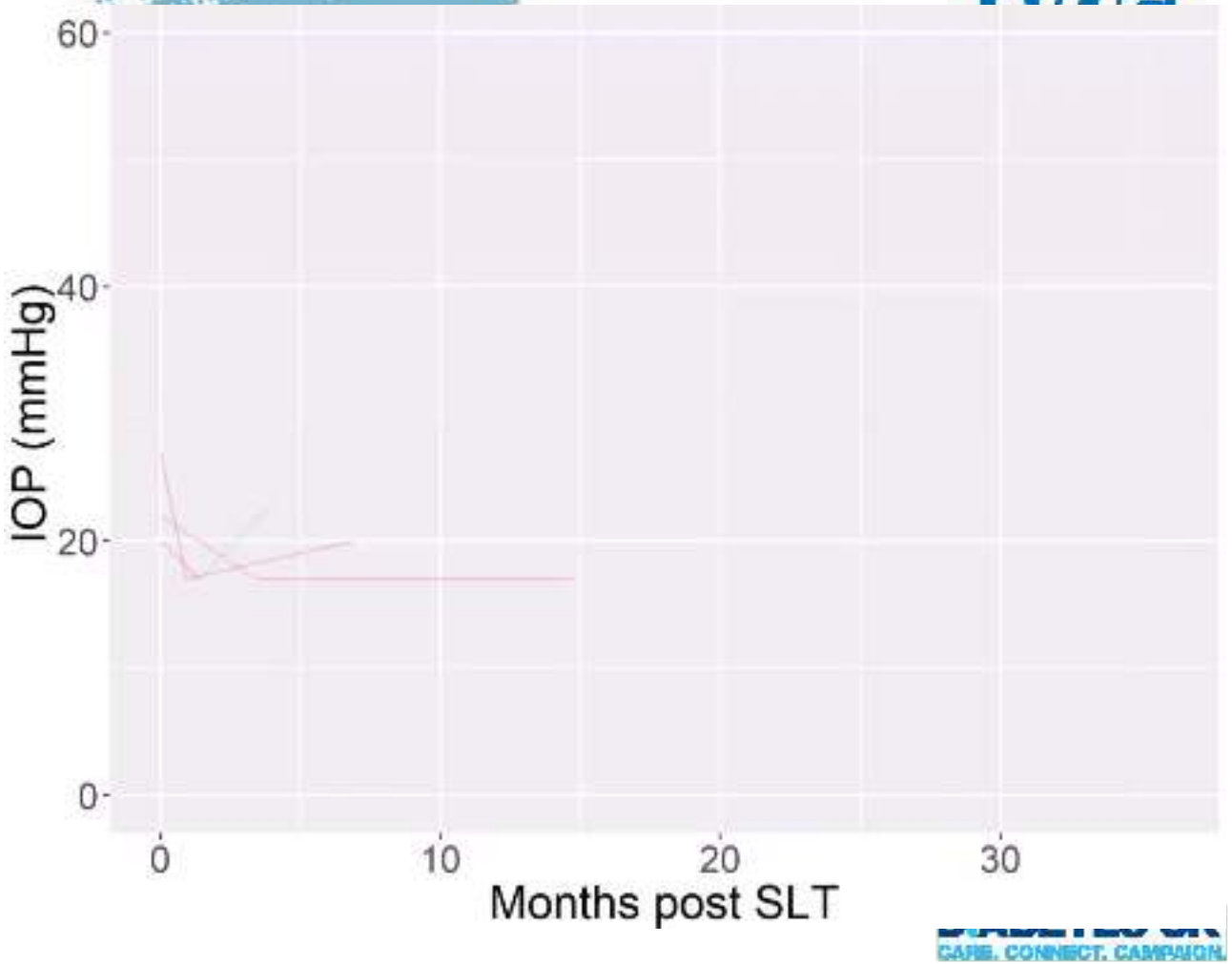


Marshall, H. N. *et al.* High Polygenic Risk Is Associated with Earlier Initiation and Escalation of Treatment in Early Primary Open-Angle Glaucoma. *Ophthalmology* **130**, 830–836 (2023).



Siggs, O. M. *et al.* Association of High Polygenic Risk With Visual Field Worsening Despite Treatment in Early Primary Open-Angle Glaucoma. *JAMA Ophthalmology* **141**, 73–77 (2023).


0
years


IOP (mmHg)
Months post SLT


vegetables
activity
food
outdoors
vegetarian
tea
sunlight
fibre
coffee
drugs
fruit
smoking
Mediterranean
drink
fat
diet
nutrition
sedentary
exercise
alcohol
medications
modify
meat

Results: caffeine ~ IOPcc

Lowest intake

Highest intake

- Q1 : Ref
- Q2 :
- Q3 :
- Q4 :
- Q5 :

***P*-trend = 0.01**

Adjusted for: age, sex, ethnicity, smoking status, frequency of alcohol intake, physical activity, deprivation index, BMI, systolic blood pressure, diabetes

Results: caffeine ~ glaucoma

Lowest intake

Highest intake

- Q1 : Ref
- Q2 :
- Q3 :
- Q4 :
- Q5 :

***P*-trend = 0.59**

Adjusted for: age, sex, ethnicity, smoking status, frequency of alcohol intake, physical activity, deprivation index, BMI, systolic blood pressure, diabetes

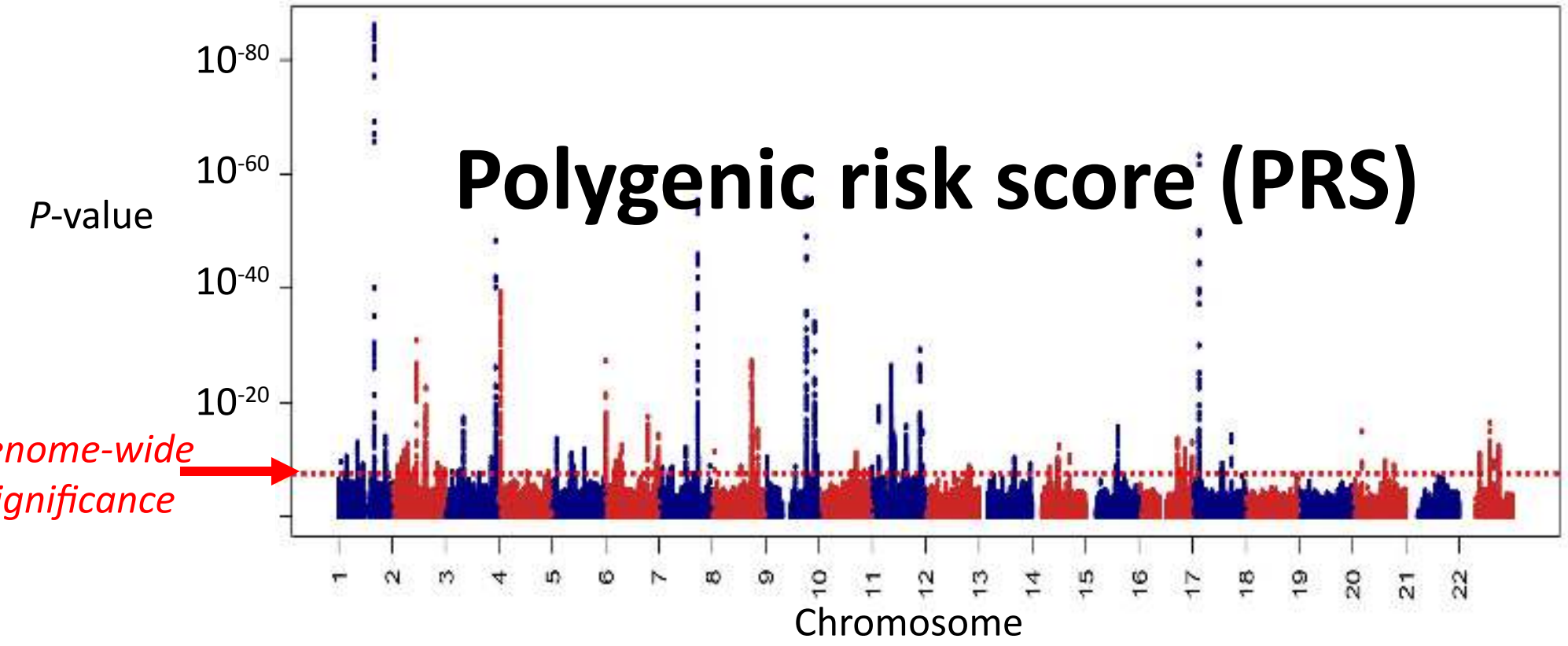
nature genetics

LETTERS

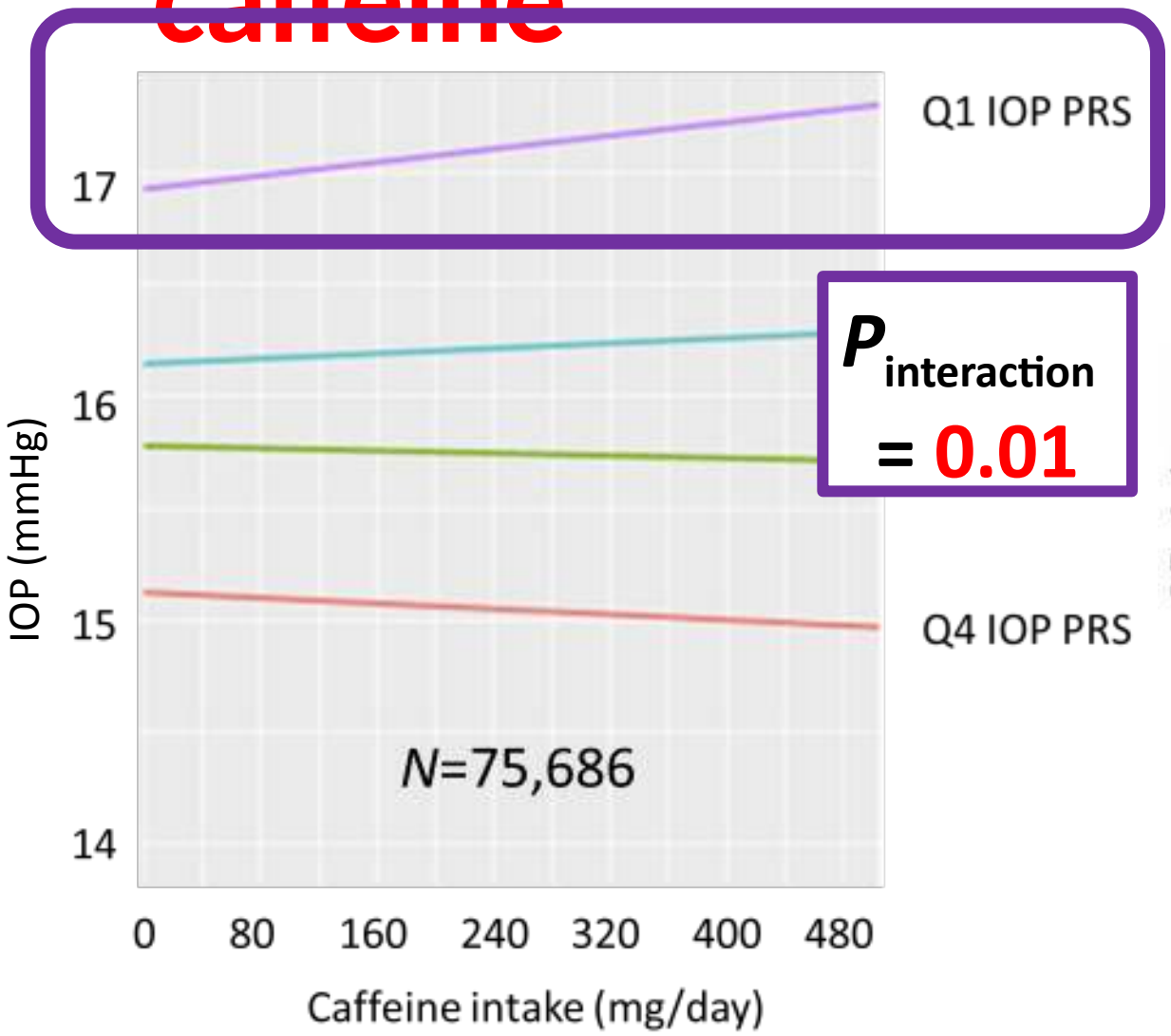
https://doi.org/10.1038/s41588-018-0126-8

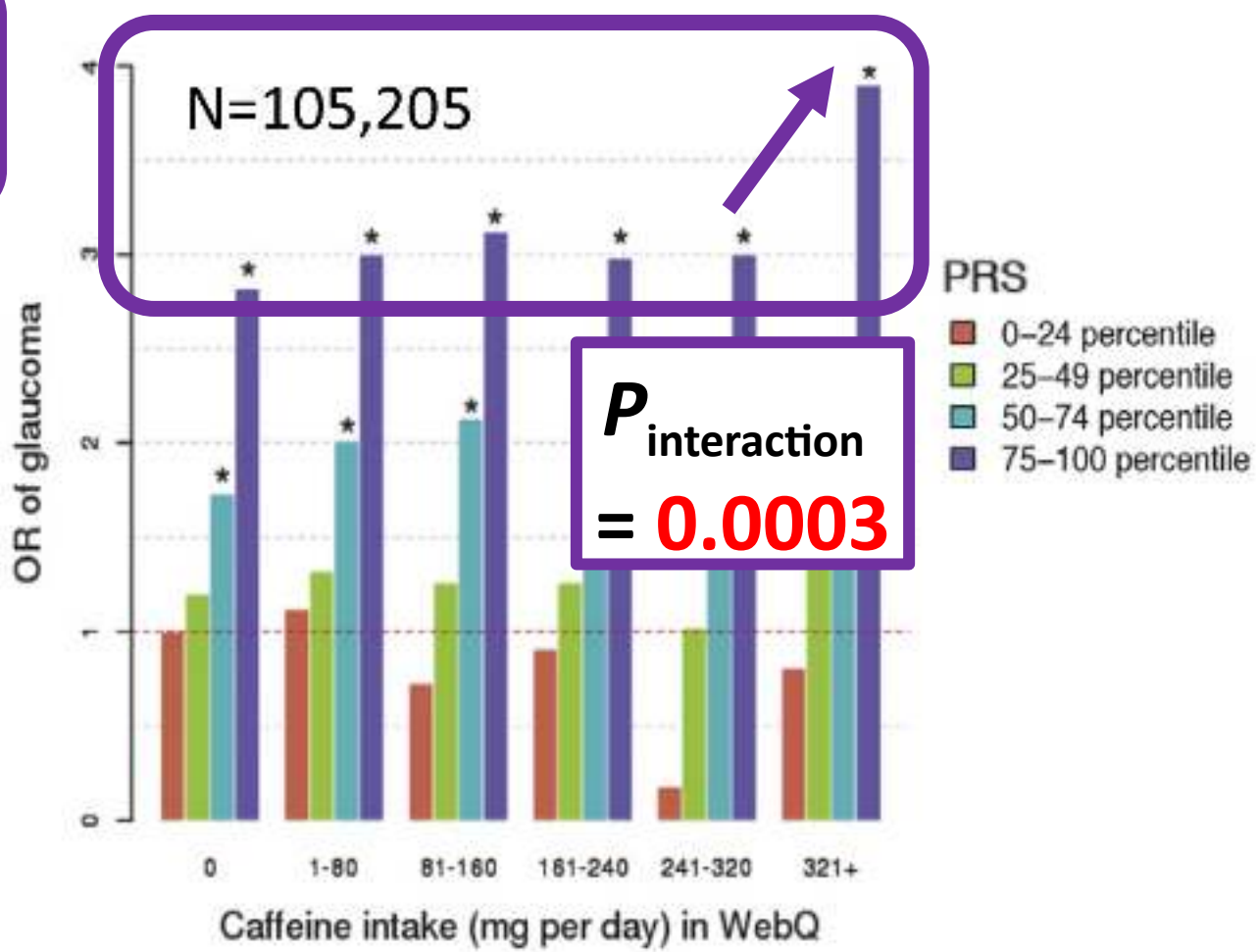
Genome-wide analyses identify 68 new loci associated with intraocular pressure and improve risk prediction for primary open-angle glaucoma

Anthony P. Khawaja[1,2,15], Jessica N. Cooke Bailey[3,15], Nicholas J. Wareham[4], Robert A. Scott[4],



Gene-environment interaction: caffeine





Kim J, Aschard H, Kang JH, et al. *Ophthalmology*. 2021;128(6):866-876

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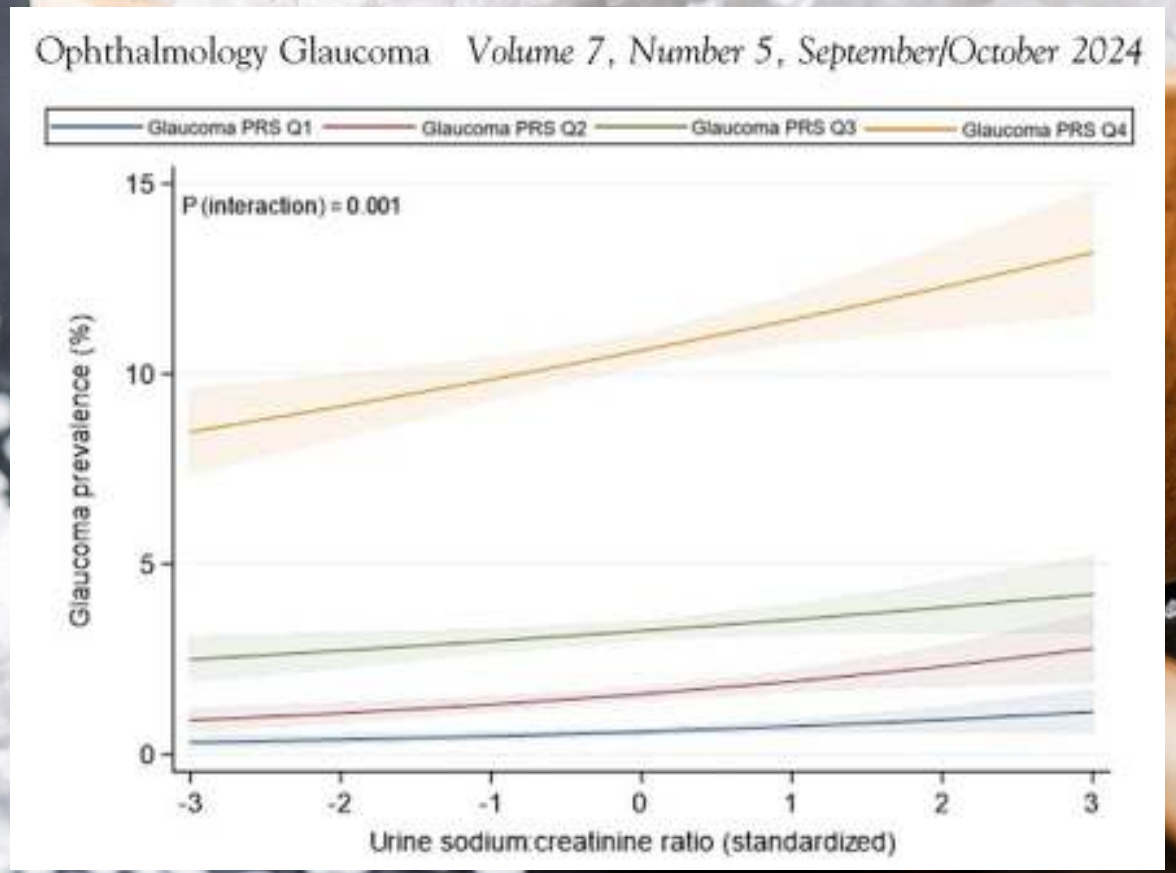
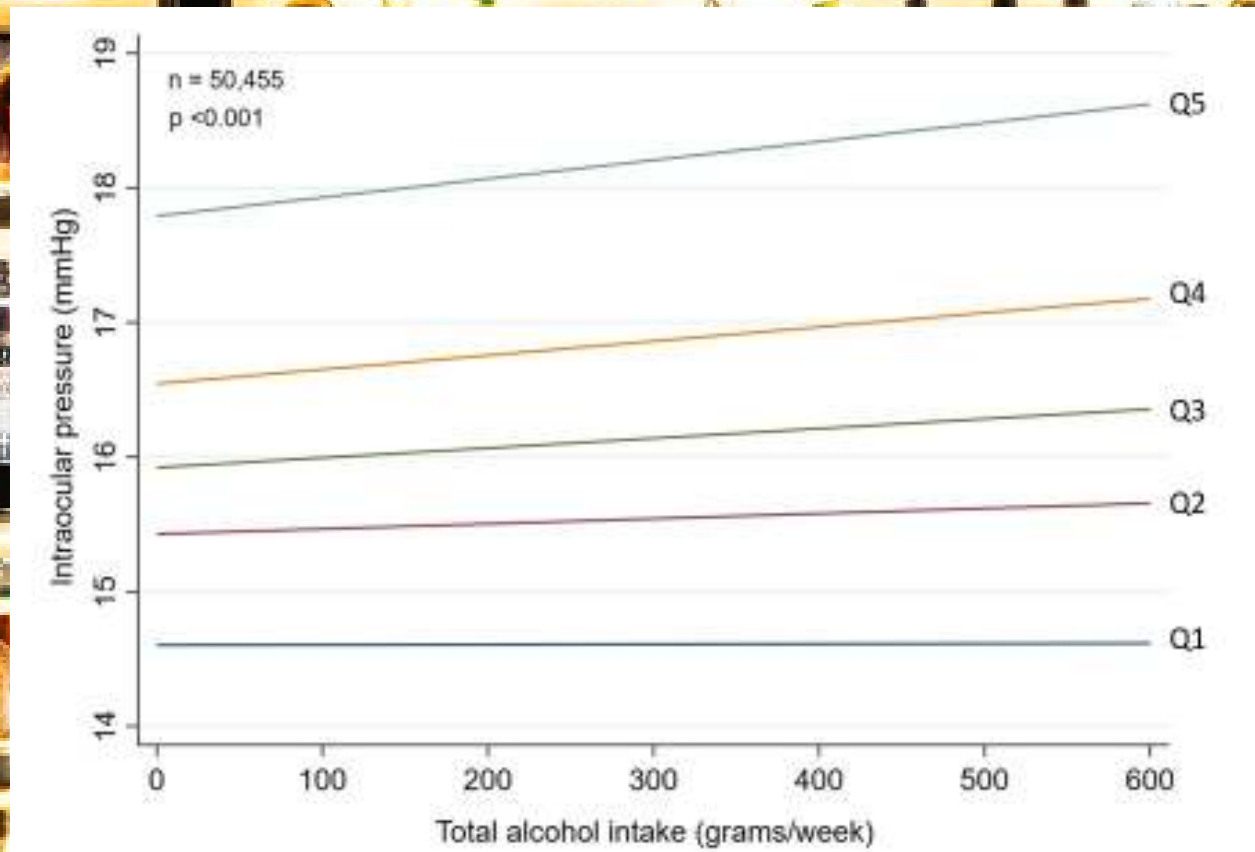




23andMe®

Glaucoma

POWERED BY 23ANDME RESEARCH

Glaucoma is a group of eye conditions that occurs when the nerve in the back of the eye (called the optic nerve) is damaged, most commonly due to high eye pressure. Optic nerve damage can cause gradual vision loss that may start as blind spots or loss of side (peripheral) vision and worsen over time.

Anthony, your genetic result is associated with a **typical likelihood** of developing glaucoma.

An estimated **15%** of people with genetics and other factors like yours develop glaucoma **by their 80s**. This is based on data from male 23andMe research participants of Northern African/Central & Western Asian descent.

This estimate is based on currently available data and may be updated over time.

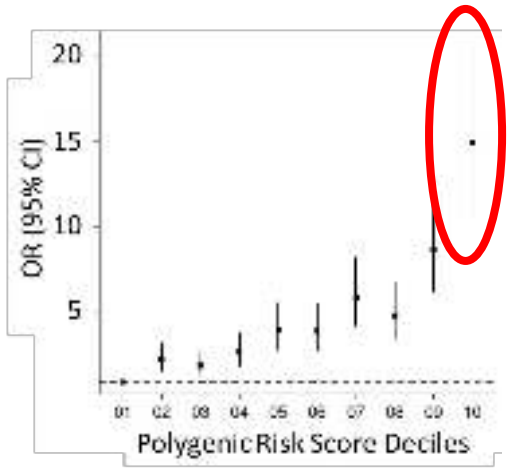
+
Our
Future
Health

£20/p

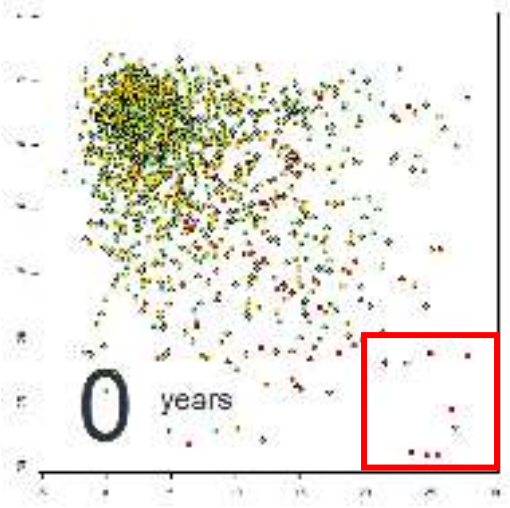
5 million adults

Genomics enabling personalised care

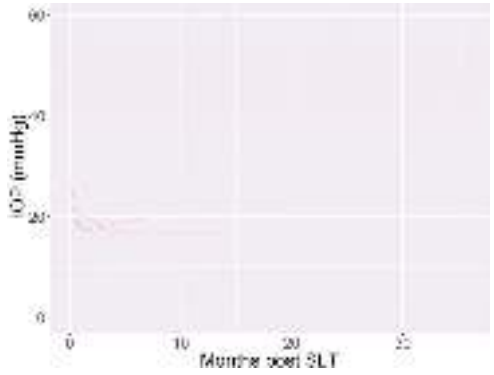
Population screening



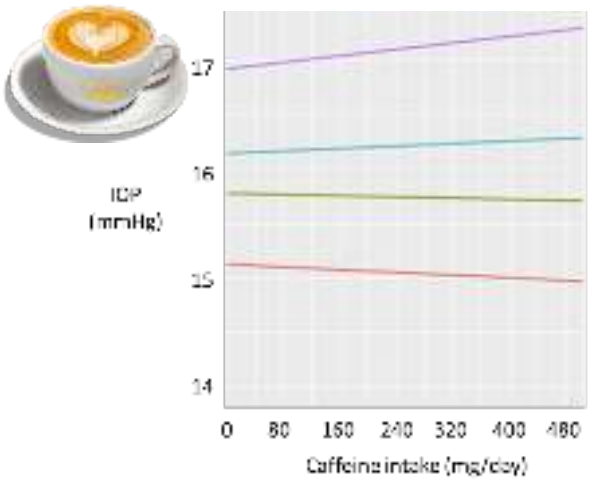
Risk stratification



Personalised treatment



Personalised lifestyle advice



Moorfields Eye Hospital NHS Foundation Trust

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Thank you

UK Research and Innovation

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Moorfields Eye Charity

The Lister Institute of Preventive Medicine

RIO 2025

312 loci

150
100
50
0
$-\log_{10}(p)$
TMCO1
CAV2
GAS7
FOXC1
ANGPT1
ARHGEF12
ADAMTS17
Chromosome
1
2
3
4
5
6
7
8
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