Personalized Medicine on a Statewide Scale

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DRI
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What is the Healthy Nevada Project?

- Large scale population genetics and health determinants study
- Recruiting as many Nevadans as possible
  - Current IRB approval is 250,000 participants
  - Current cohort = ~47,000 sequenced individuals
- Two components:
  - Clinical
    - Reporting on Incidental Findings - currently, CDC Tier 1
    - Risk awareness of **autosomal dominant** inherited conditions
  - Research
    - Investigator focused
    - Leveraging a data-lake of health determinants

Health Determinants

Socioeconomics

40%

Genetics

WES

Behavior

30%

Clinical Care

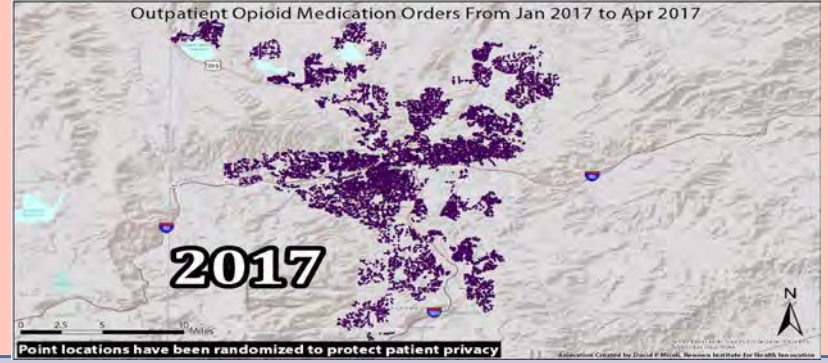
20%

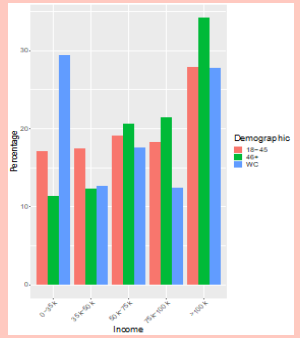
Environmental Impacts

10%

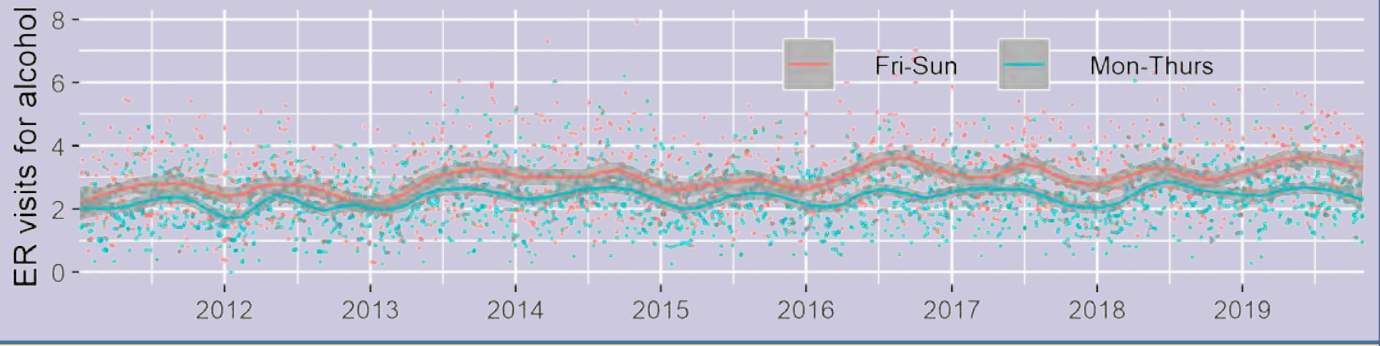
Health Outcomes

(a)





(b)



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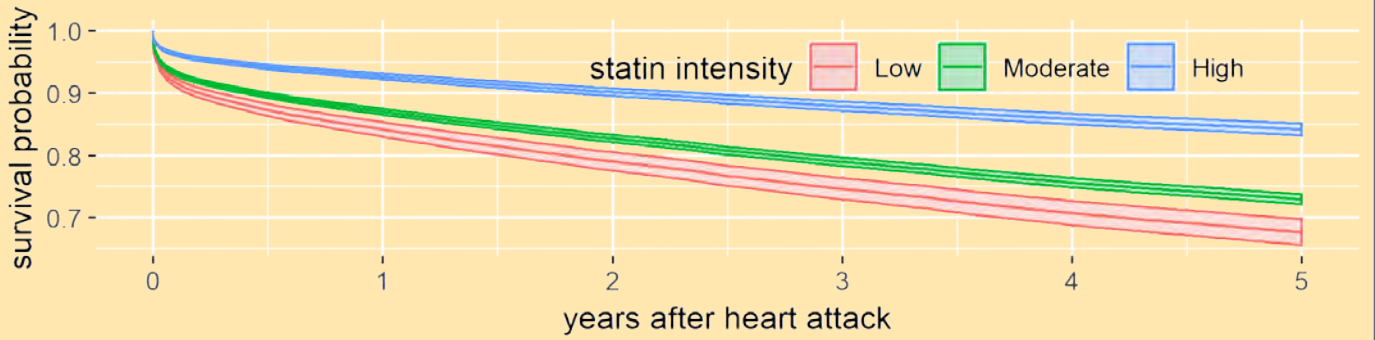

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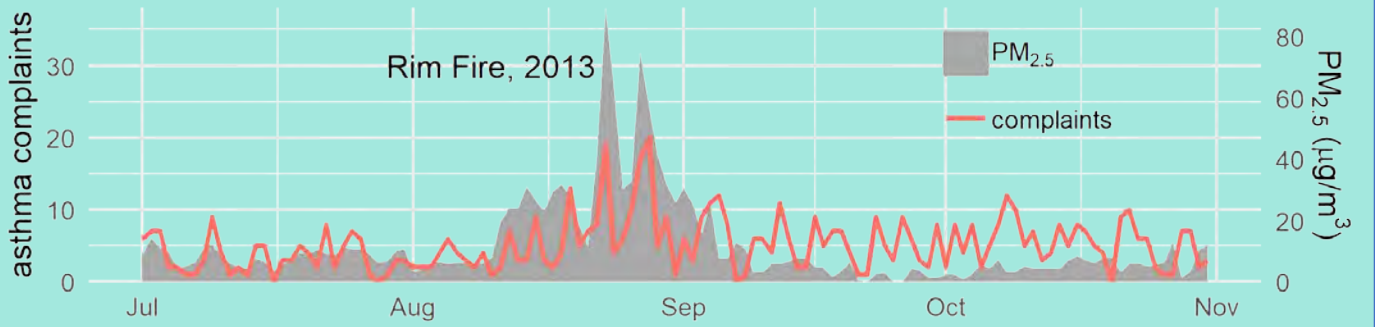
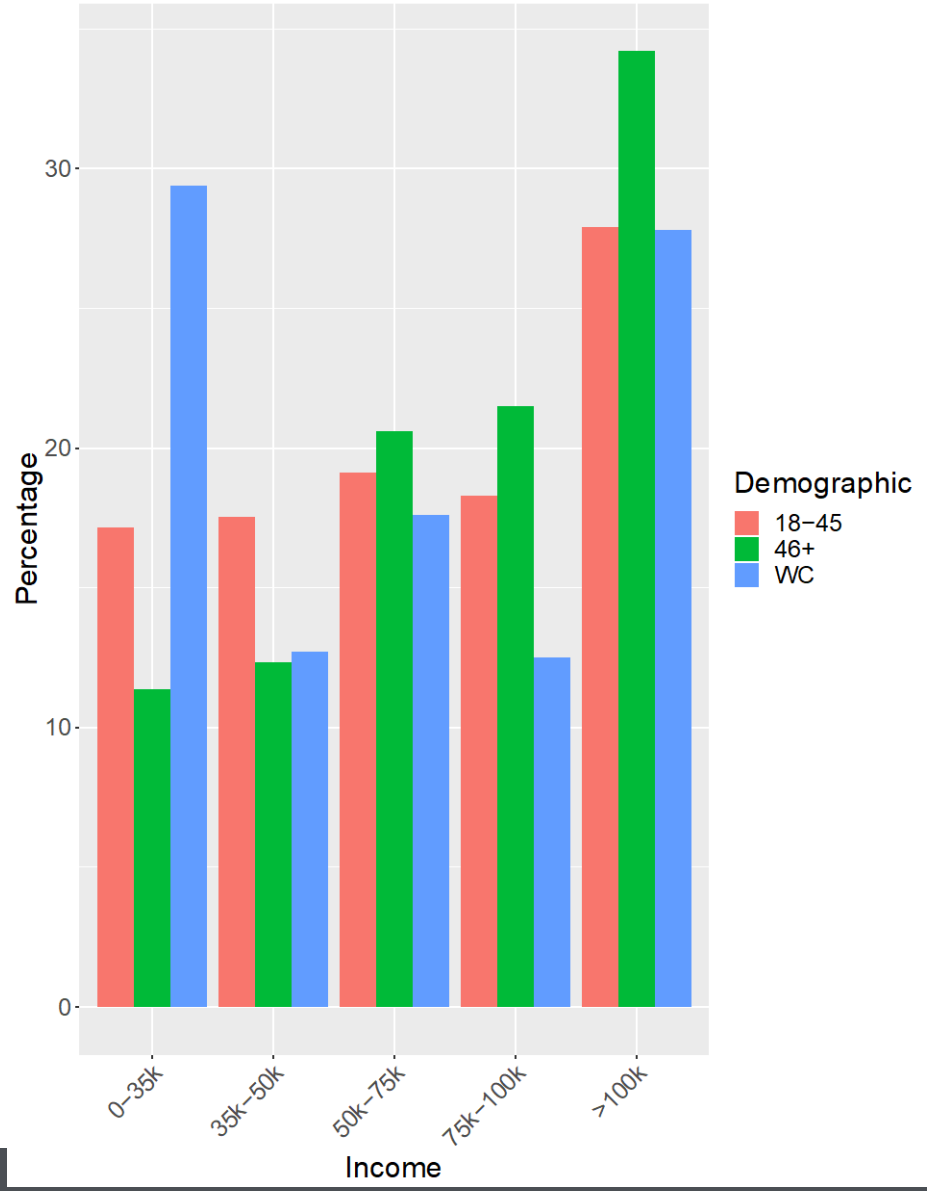


Self-reported demographics

- 30% reside in five most impoverished zip codes in Reno/Sparks
- 47% of zip codes in NV represented



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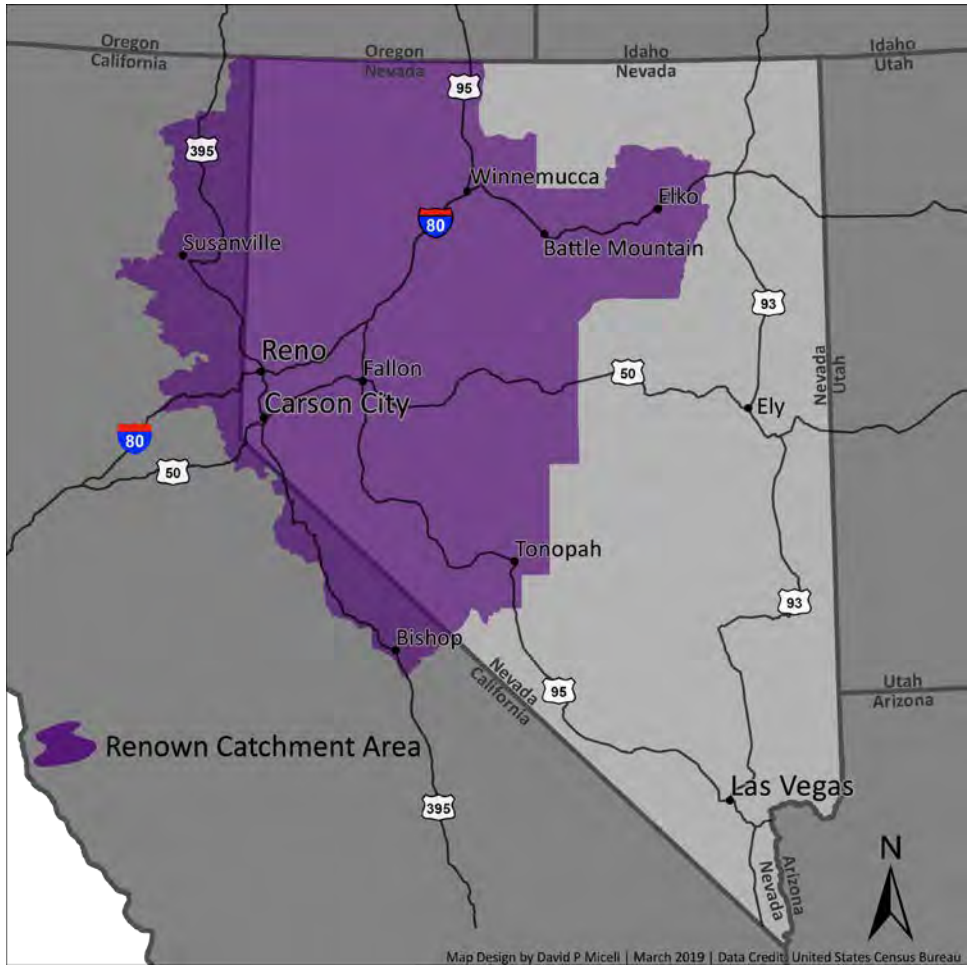
Northern Nevada is a unique catchment for studying population health

- One primary hospital system
- Multi-generational population
- >1 M Patient EHR since 2007
- 600k person catchment area
- 62k square miles



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Healthy Nevada Project structure

3 CONSENTS: STUDY, RECONTACT, RESULTS

SURVEY PLATFORM: BEHAVIOR/ SOCIAL

RECALL: BLOOD/IMAGING

RETURN OF RESULTS

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Recruitment Pathways

OUTREACH VIA PHONE

OUTREACH VIA EMAIL

EVENTS/POP-UPS

TOUCH POINTS VIA RENOWN SYSTEM

Necessity of Tier 1 population screening

- Are we effectively ascertaining Tier 1 cases using best practices?
- Are there outcome improvements of broad-based screening?
- How to accomplish population level screening?
  - Without bias
  - Effective results disclosure / follow up
  - Limit false positives

nature medicine

Letter | Published: 27 July 2020

Population genetic screening efficiently identifies carriers of autosomal dominant diseases

J. J. Grzymski ✉, G. Elhanan, J. A. Morales Rosado, E. Smith, K. A. Schlauch, R. Read, C. Rowan, N. Slotnick, S. Dabe, W. J. Metcalf, B. Lipp, H. Reed, L. Sharma, E. Levin, J. Kao, M. Rashkin, J. Bowes, K. Dunaway, A. Slonim, N. Washington, M. Ferber, A. Bolze & J. T. Lu ✉

Nature Medicine **26**, 1235–1239(2020) | Cite this article

CDC Tier 1 Findings:

- 1:80 prevalence of known pathogenic/likely pathogenic findings
- 26,906 participants Exome+ results
- Results analyzed for 358 carriers (no correction for relatedness)
  - Hereditary Breast and Ovarian Cancer Syndrome (HBOC): 178 (1:150)
  - Lynch Syndrome: 80 (1:340)
  - Familial Hypercholesterolemia: 102 (1:260)

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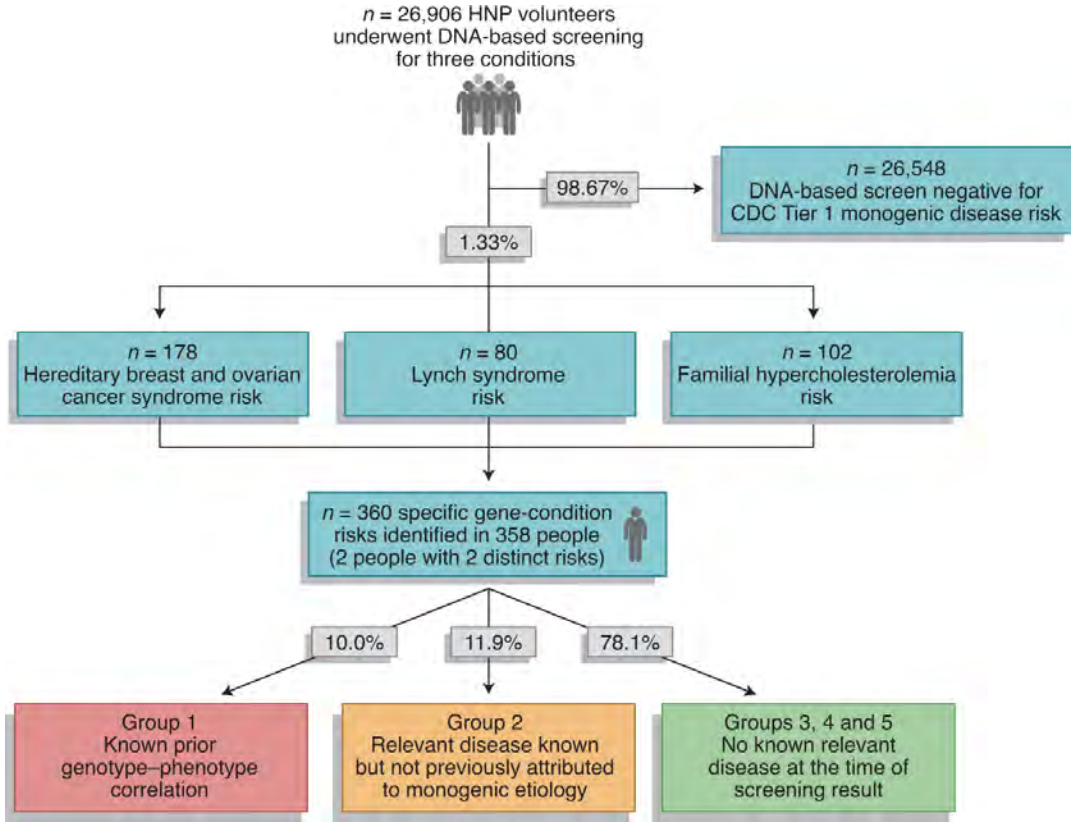
Majority of patients do not have known family history of disease

90% of participants screening positive were not previously identified

19.8% of these had documentation in their medical records of inherited genetic disease risk, including family history



Murray and Giovanni, 2020

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Case Study 1

Female 64y/o

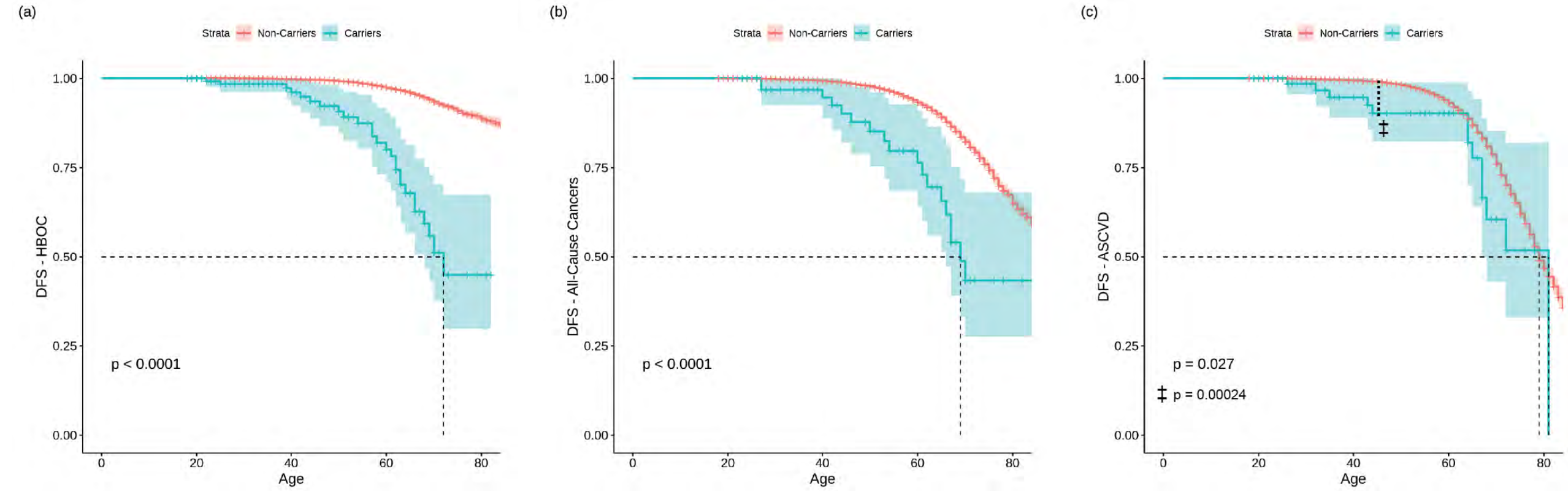
- *BRCA1*
- Rt. Ovarian malignancy (dx @ 63y/o)
- Secondary spread to large intestine and retroperitoneum as well as malignant pleural effusion
- Scant evidence of prior mammography (1x, 6Y before diagnosis)
- No medical record documentation of family history
- No medical documentation of *BRCA1*

Case Study 2

Male 28y/o

- Lynch (*MSH2*)
- Metastatic colon cancer (dx @26)
- Family history of digestive organs and bladder malignancies.
- No medical record documentation of genetic diagnosis.

Why we need to ascertain CDC Tier 1 carrier status



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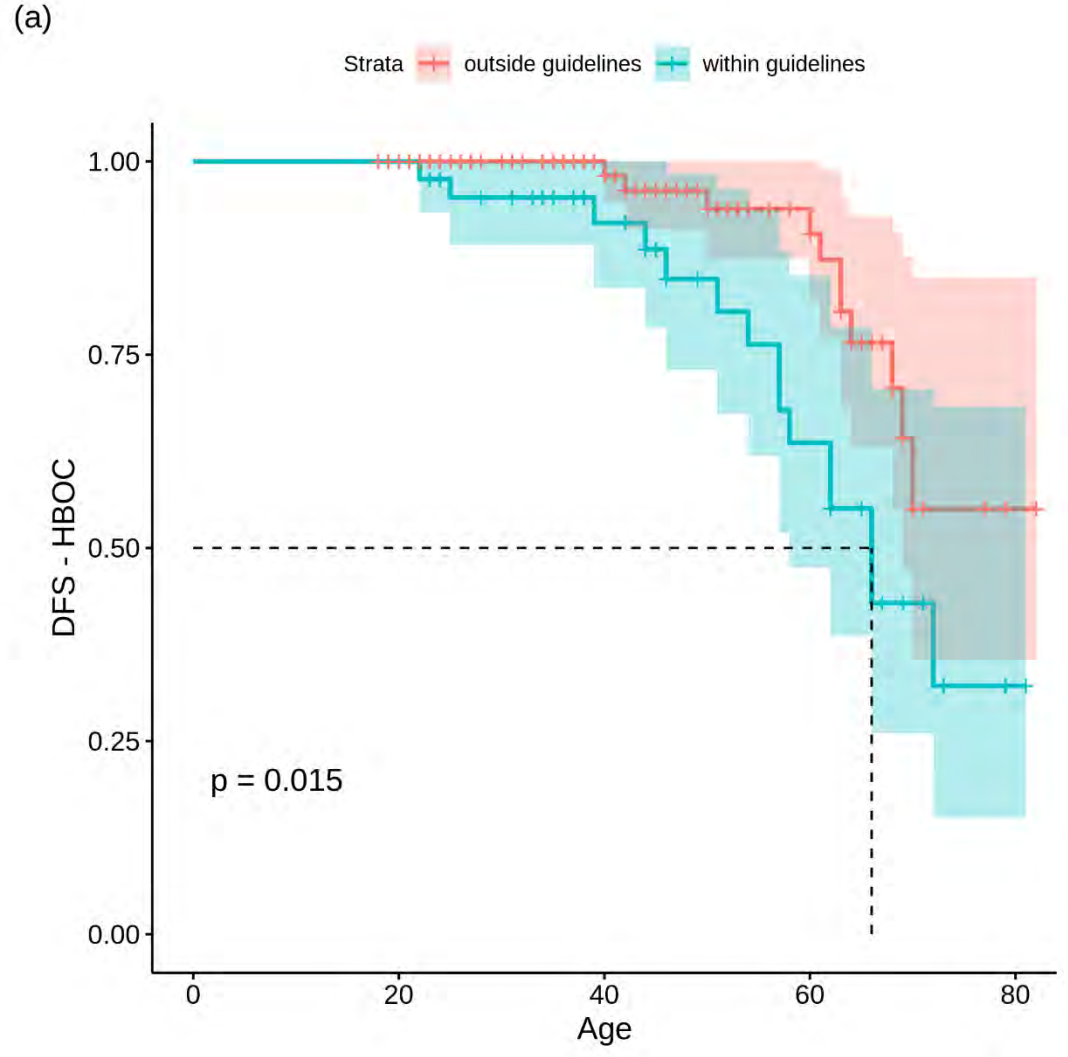
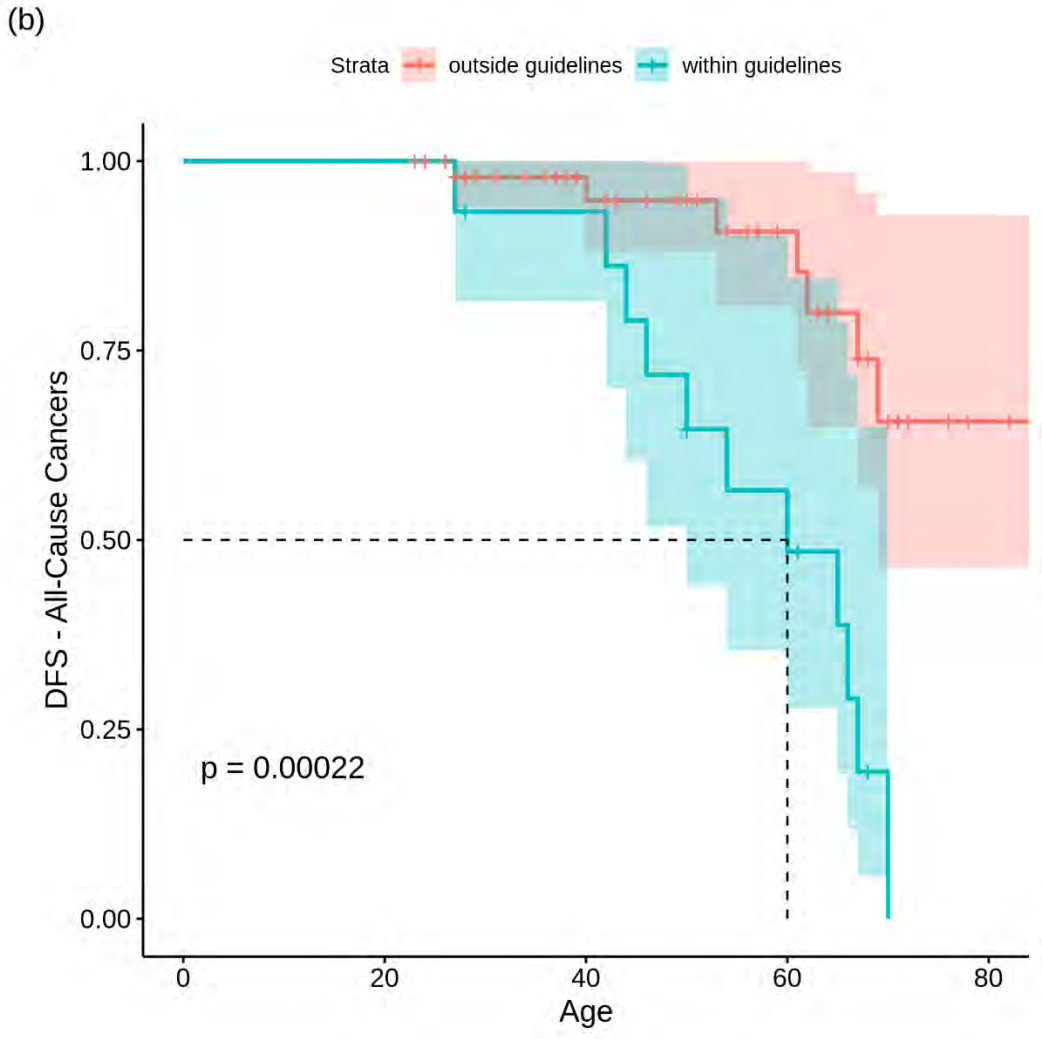
But, falling within guidelines confers excess risk





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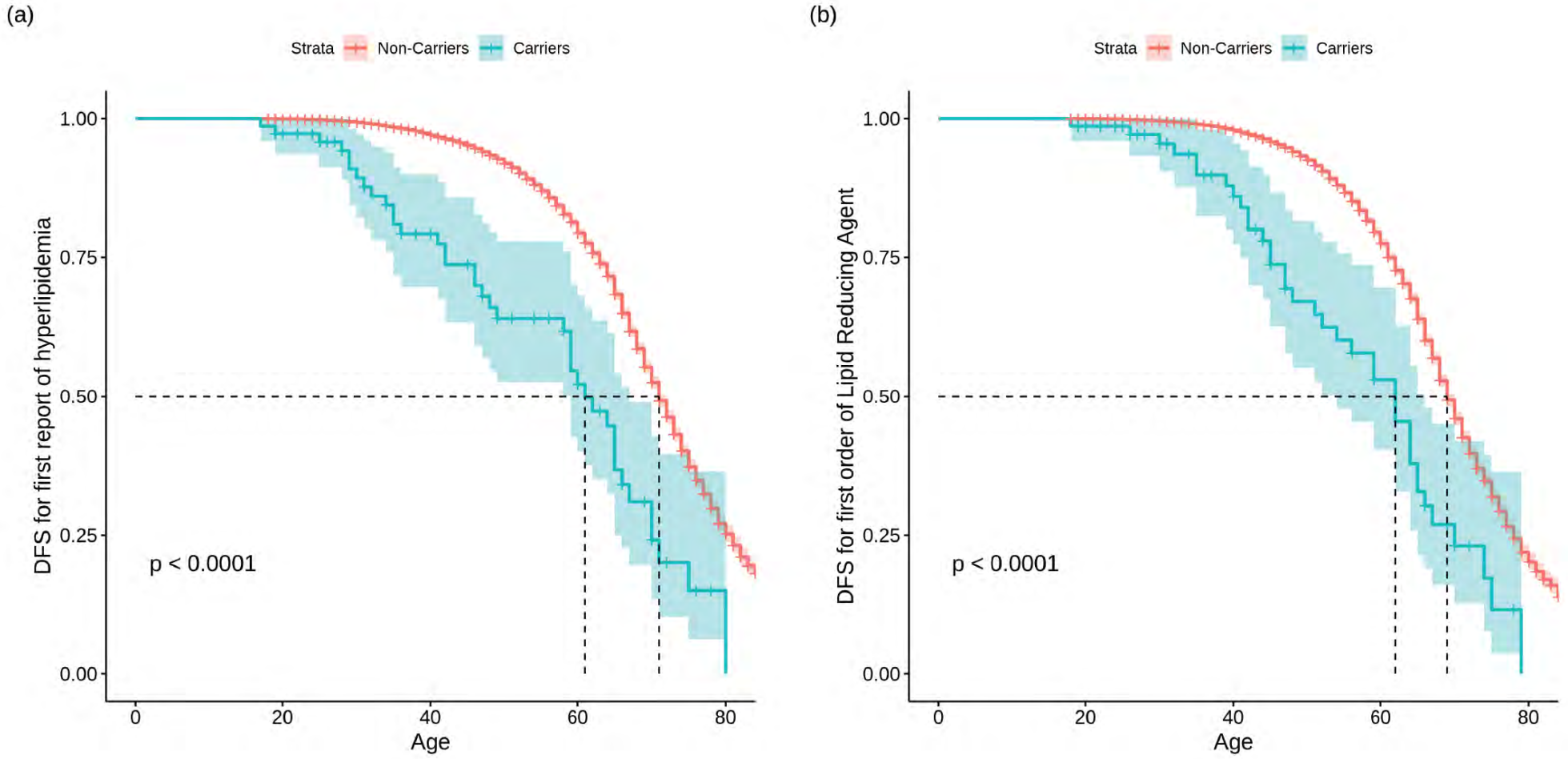
Earlier intervention for ASCVD based on lipid screening?



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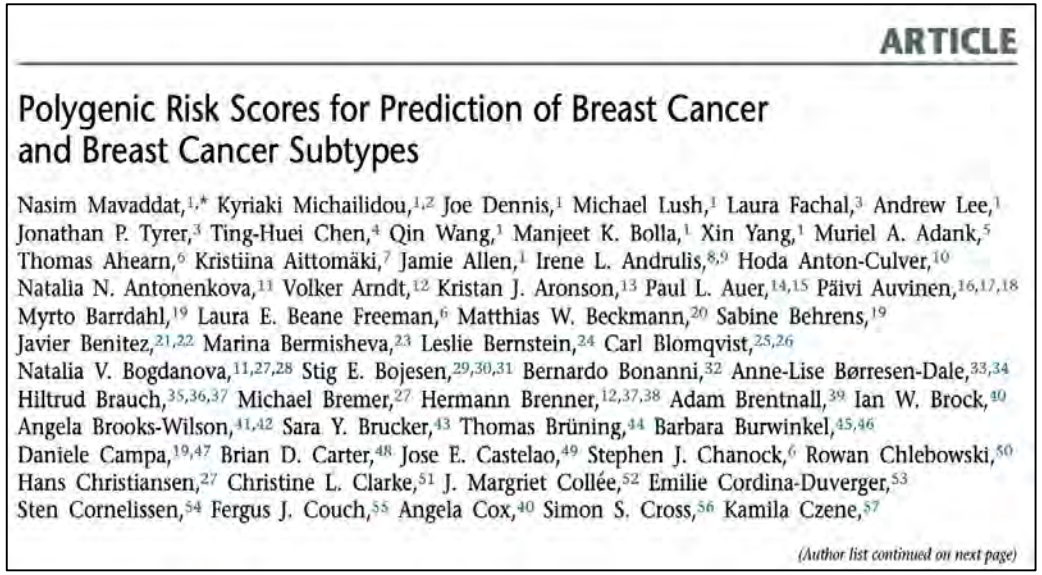
Overall results return (updated since paper)

	HBOC & LYNCH	FH
Informed of Results	231	143
Results pending delivery	72	68
Results Lost to Follow Up	23	20
Total Results not received	95	88
Totals	326	231

>98% consent to return of results, yet 70% success rate returning results

Future steps



ARTICLE

Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes

Nasim Mavaddat,[1,*] Kyriaki Michailidou,[1,2] Joe Dennis,[1] Michael Lush,[1] Laura Fachal,[3] Andrew Lee,[1] Jonathan P. Tyrer,[3] Ting-Huei Chen,[4] Qin Wang,[1] Manjeet K. Bolla,[1] Xin Yang,[1] Muriel A. Adank,[5] Thomas Ahearn,[6] Kristiina Aittomäki,[7] Jamie Allen,[1] Irene L. Andrulis,[8,9] Hoda Anton-Culver,[10] Natalia N. Antonenkova,[11] Volker Arndt,[12] Kristan J. Aronson,[13] Paul L. Auer,[14,15] Päivi Auvinen,[16,17,18] Myrto Barrdahl,[19] Laura E. Beane Freeman,[6] Matthias W. Beckmann,[20] Sabine Behrens,[19] Javier Benitez,[21,22] Marina Bermisheva,[23] Leslie Bernstein,[24] Carl Blomqvist,[25,26] Natalia V. Bogdanova,[11,27,28] Stig E. Bojesen,[29,30,31] Bernardo Bonanni,[32] Anne-Lise Børresen-Dale,[33,34] Hiltrud Brauch,[35,36,37] Michael Bremer,[27] Hermann Brenner,[12,37,38] Adam Brentnall,[39] Ian W. Brock,[40] Angela Brooks-Wilson,[41,42] Sara Y. Brucker,[43] Thomas Brüning,[44] Barbara Burwinkel,[45,46] Daniele Campa,[19,47] Brian D. Carter,[48] Jose E. Castelao,[49] Stephen J. Chanock,[6] Rowan Chlebowski,[50] Hans Christiansen,[27] Christine L. Clarke,[51] J. Margriet Collée,[52] Emilie Cordina-Duverger,[53] Sten Cornelissen,[54] Fergus J. Couch,[55] Angela Cox,[40] Simon S. Cross,[56] Kamila Czene,[57]

(Author list continued on next page)

- Used a 313 SNPs PGS from Mavaddat et al., AJHG, 2019
- Score was calculated using SNPs directly sequenced or imputed
- All participants were assigned to one genetic ancestry (6 different groups total) based on ADMIXTURE results
- Distributions were made for each genetic ancestry group
- Participants were assigned a polygenic risk based on the distribution of the scores for their specific genetic ancestry

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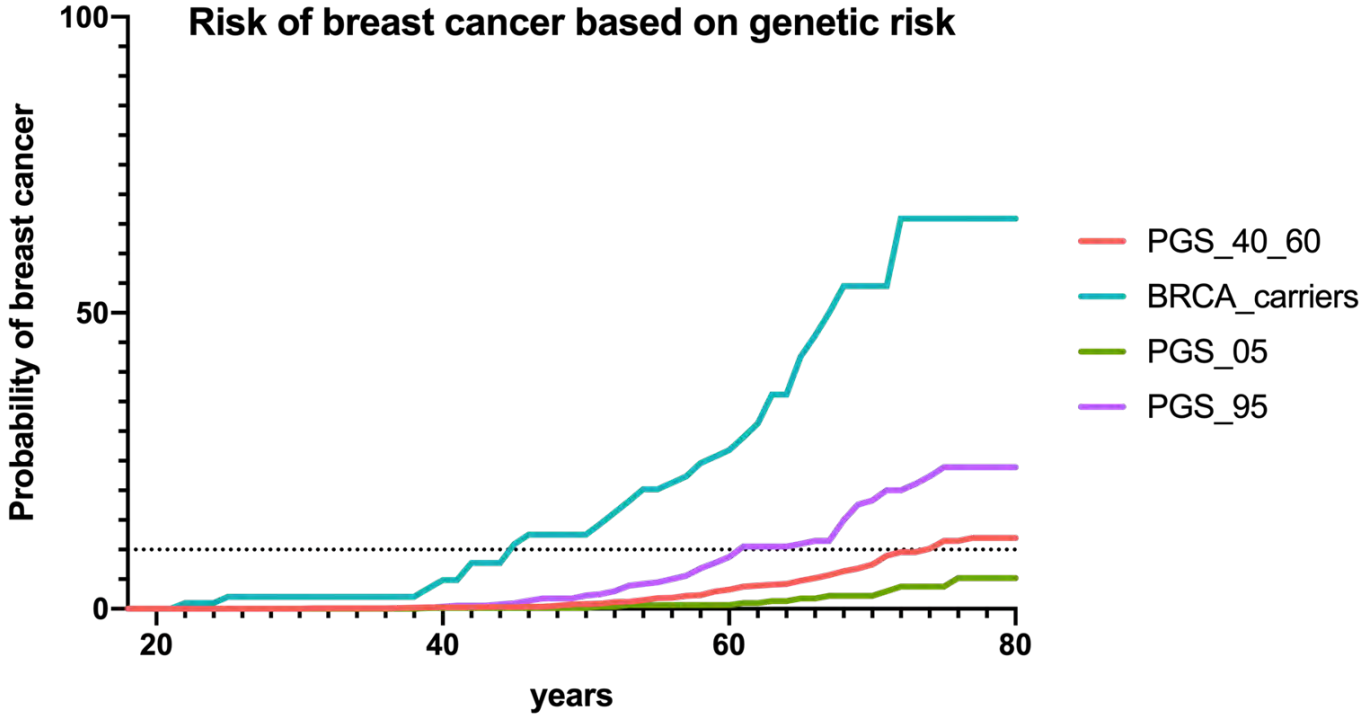
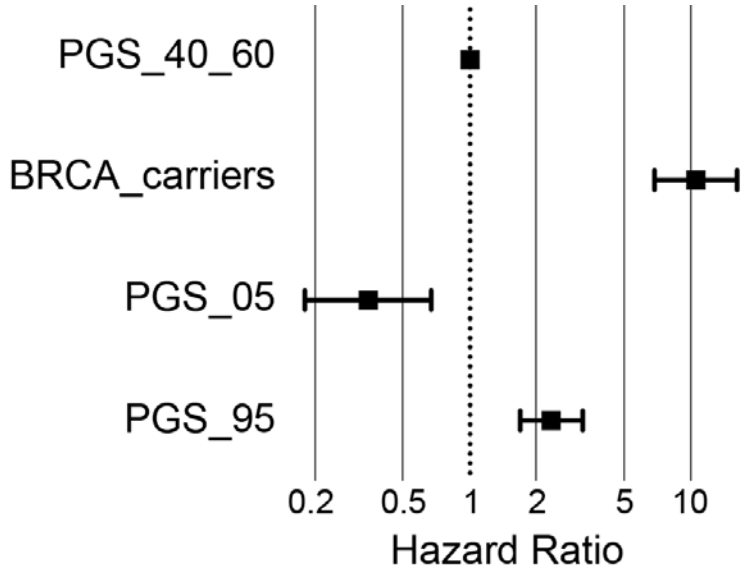
High polygenic risk for breast cancer is in-between monogenic risk and average risk





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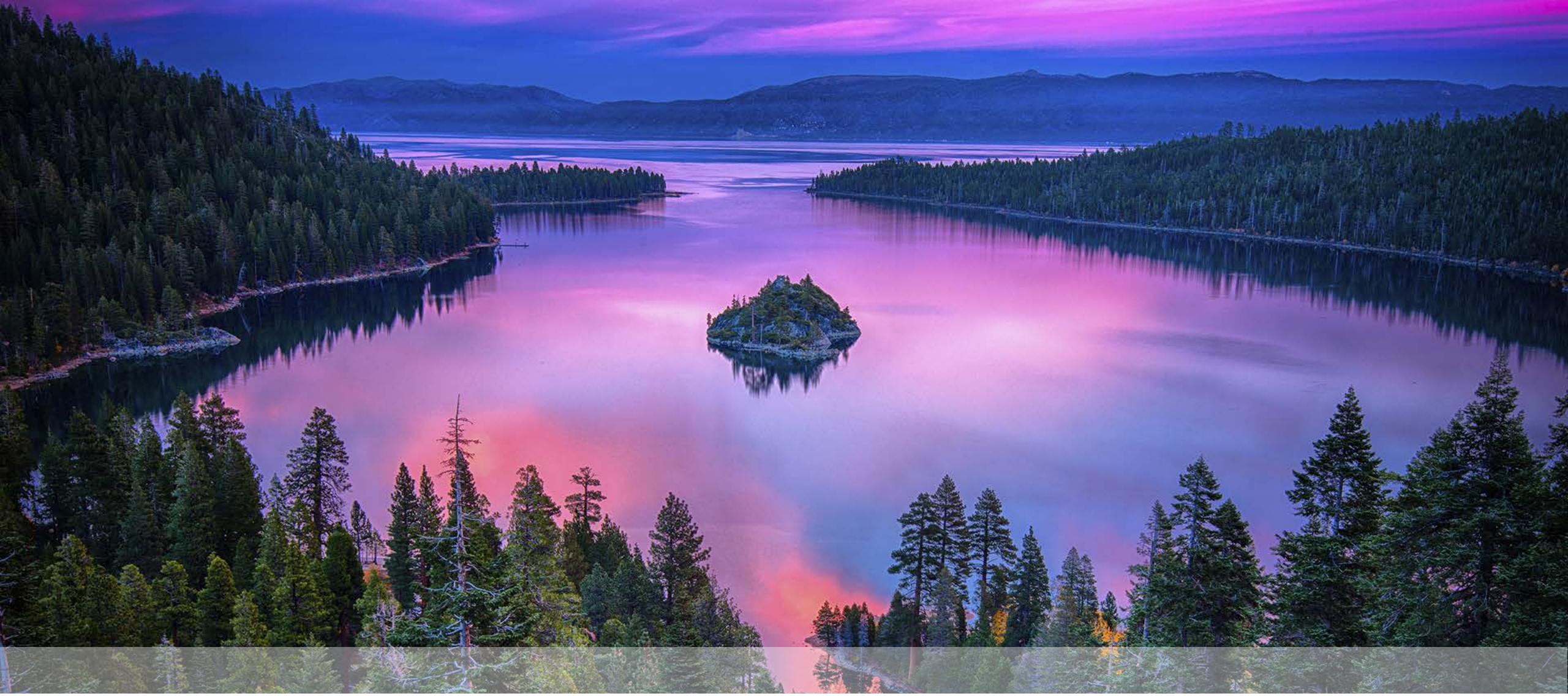

Questions

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