Cost-Effectiveness of Population Genomic Screening

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David Veenstra

- Consultant Illumina, Exact Sciences
- Research funding GeneDx

Reimbursement for healthcare technologies

1. Increasing push for value in healthcare
2. Difficult to quantify, but established methods
3. Approaches are evolving to capture broader aspects of value
4. In the US, formal cost-effectiveness analyses do not directly influence reimbursement decisions, but provide context and inform discussions

How do we assess long-term impacts?

- RCTs would need to be prohibitively large given relatively low prevalence of conditions
- Follow-up period likely would need to be decades

Decision modeling

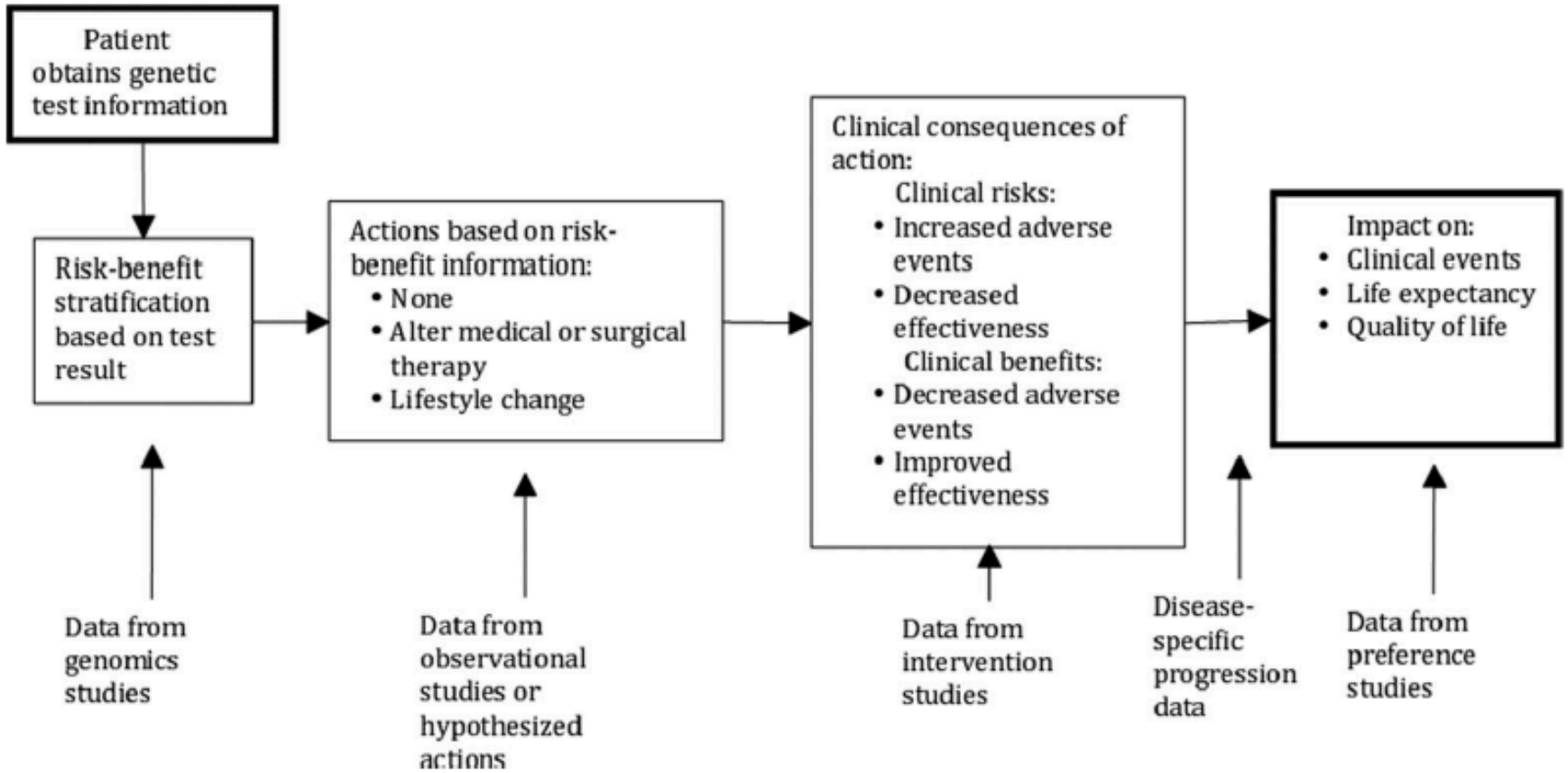


Fig. 1. Schematic diagram of disease-based model.

USPSTF and decision modeling

Annals of Internal Medicine RESEARCH AND REPORTING METHODS

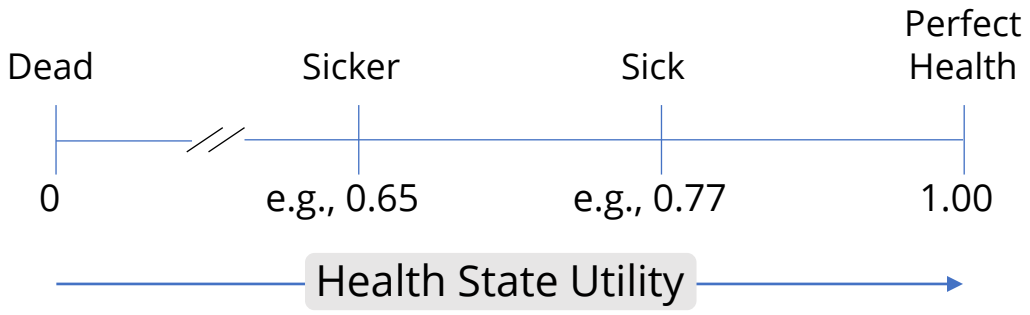
Use of Decision Models in the Development of Evidence-Based Clinical Preventive Services Recommendations: Methods of the U.S. Preventive Services Task Force

Douglas K. Owens, MD, MS; Evelyn P. Whitlock, MD, MPH; Jillian Henderson, PhD, MPH; Michael P. Pignone, MD, MPH; Alex H. Krist, MD, MPH; Kirsten Bibbins-Domingo, PhD, MD, MAS; Susan J. Curry, PhD; Karina W. Davidson, PhD, MASc; Mark Ebell, MD, MS; Matthew W. Gillman, MD, SM; David C. Grossman, MD, MPH; Alex R. Kemper, MD, MPH, MS; Ann E. Kurth, PhD, RN, MSN, MPH; Michael Maciosek, PhD; Albert L. Siu, MD, MSPH; and Michael L. LeFevre, MD, MPH; on behalf of the U.S. Preventive Services Task Force*

Ann Int Med 2016

Health Economics Primer

- Given limited health care budgets, choose the intervention that provides the most health per dollar spent.
- Modeling is used to synthesize clinical data with real world burden of disease outcomes (cost, quality of life) to estimate the lifetime costs and health impacts of a clinical decision.



QALY= Quality-Adjusted Life Year

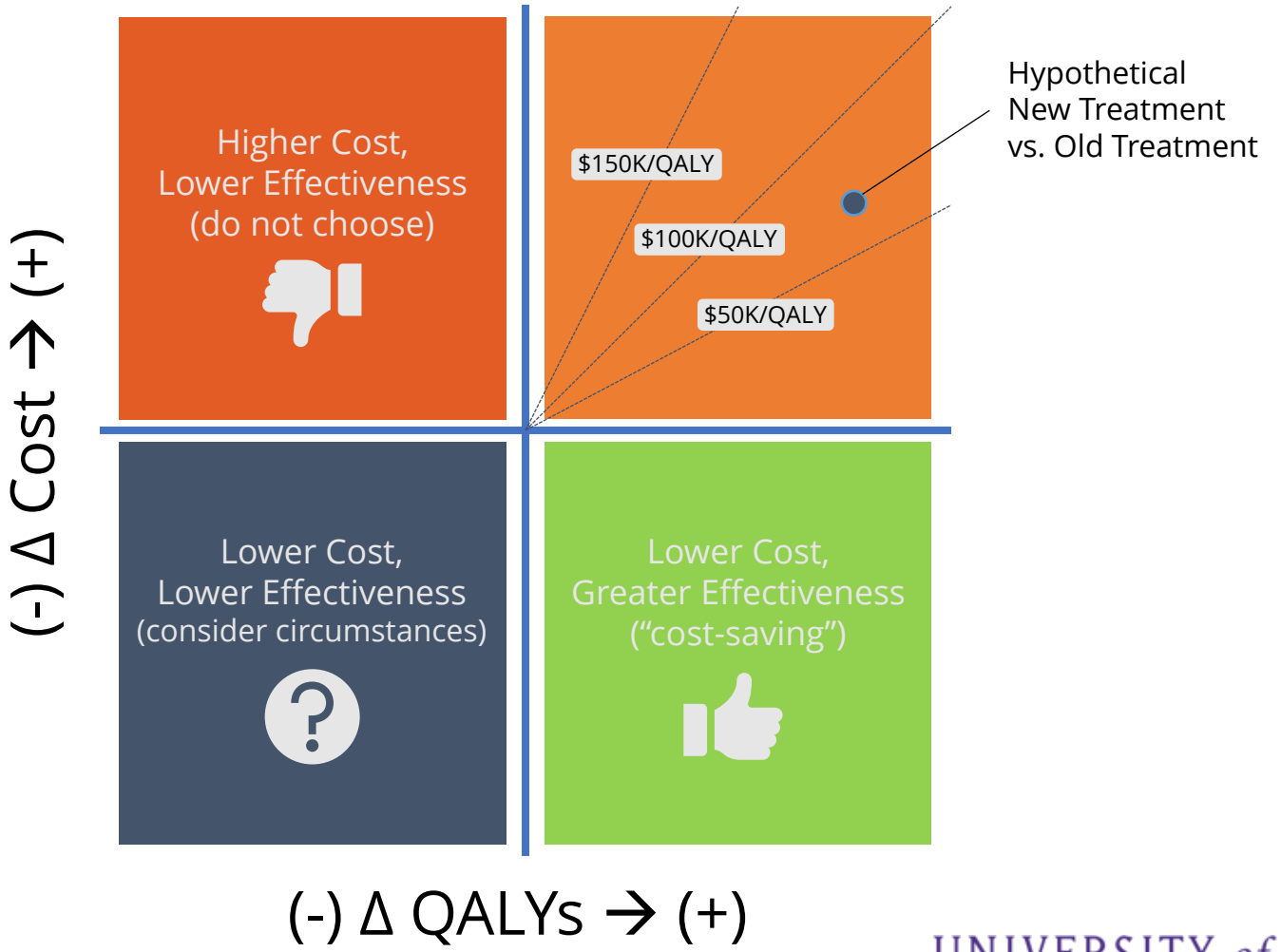
example: 3 sick years + 2 sicker years:

3*0.77 + 2*0.65 = 3.61 QALYs

Incremental Cost-Effectiveness Ratio (ICER) $= \frac{(Cost_{(new\ Tx)} - Cost_{(old\ Tx)})}{(QALYs_{(new\ Tx)} - QALYs_{(old\ Tx)})}$

In the US, "acceptable" cost-effectiveness ratios ≈ $50K - $150K

Cost-Effectiveness



We screen newborns, don’t we?

Jim Evans et al, GIM 2013

Annals of Internal Medicine

ORIGINAL RESEARCH

Population Genomic Screening for Three Common Hereditary Conditions

A Cost-Effectiveness Analysis

Gregory F. Guzauskas, MSPH, PhD; Shawn Garbett, MS; Zilu Zhou, MPH; Jonathan S. Schildcrout, PhD; John A. Graves, PhD; Marc S. Williams, MD; Jing Hao, PhD, MD, MS, MPH; Laney K. Jones, PharmD, MPH; Scott J. Spencer, MPA, MA, PhD; Shangqing Jiang, MPH; David L. Veenstra, PharmD, PhD*; and Josh F. Peterson, MD, MPH*

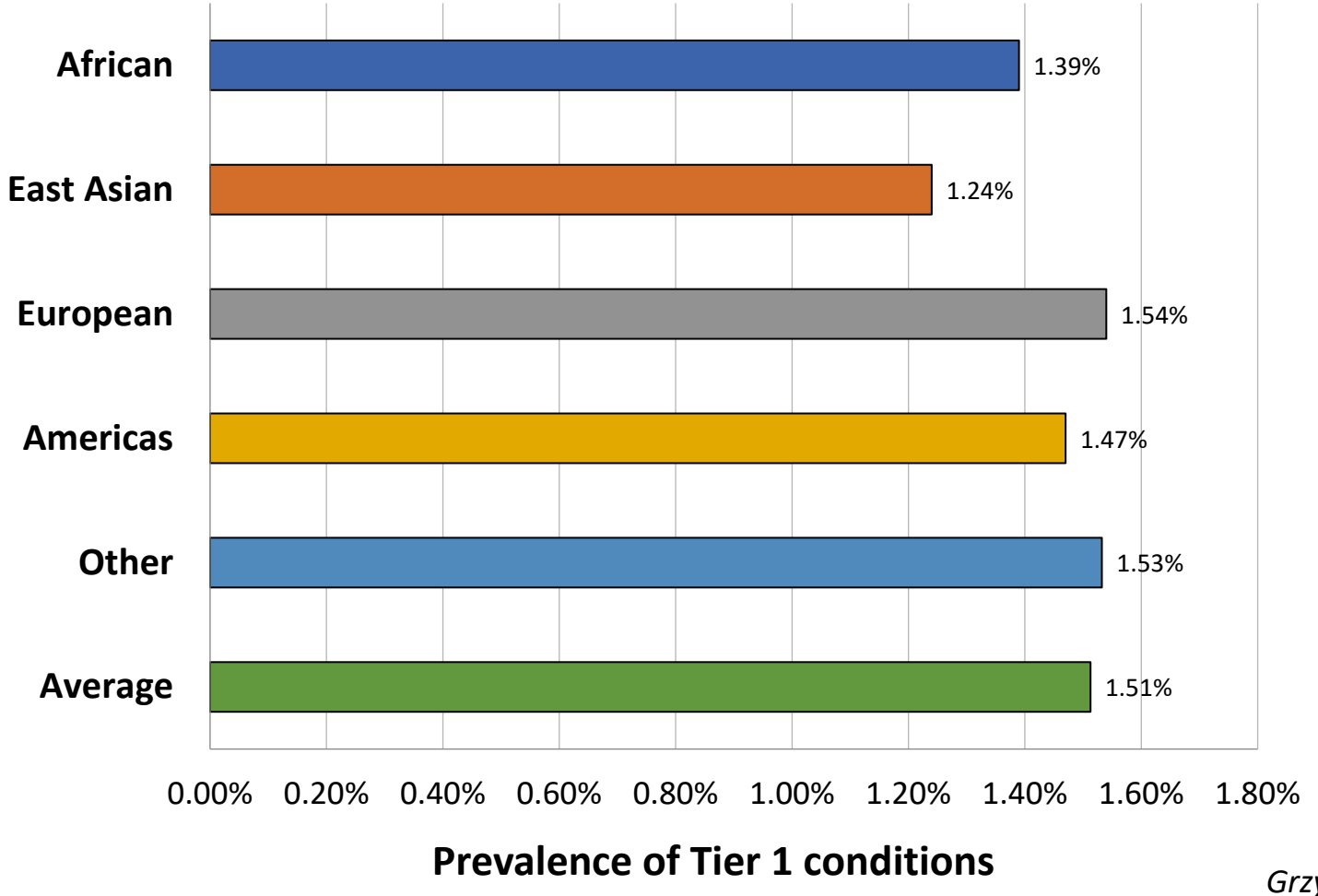
CDC Tier 1 Conditions

Tier 1 Condition	Increased Risk For:	Risk-Reduction
Hereditary Breast and Ovarian Cancer	**Breast cancer, Ovarian cancer,** Other cancers	Mammography + MRI, Mastectomy, Salpingo-Oophorectomy
Lynch Syndrome	**Colorectal cancer,** Endometrial cancer, Other cancers	Increased colonoscopy surveillance
Familial hypercholesterolemia	**Myocardial infarction, Stroke**	Moderate to high-intensity statin therapy

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm

Prevalence across ancestries



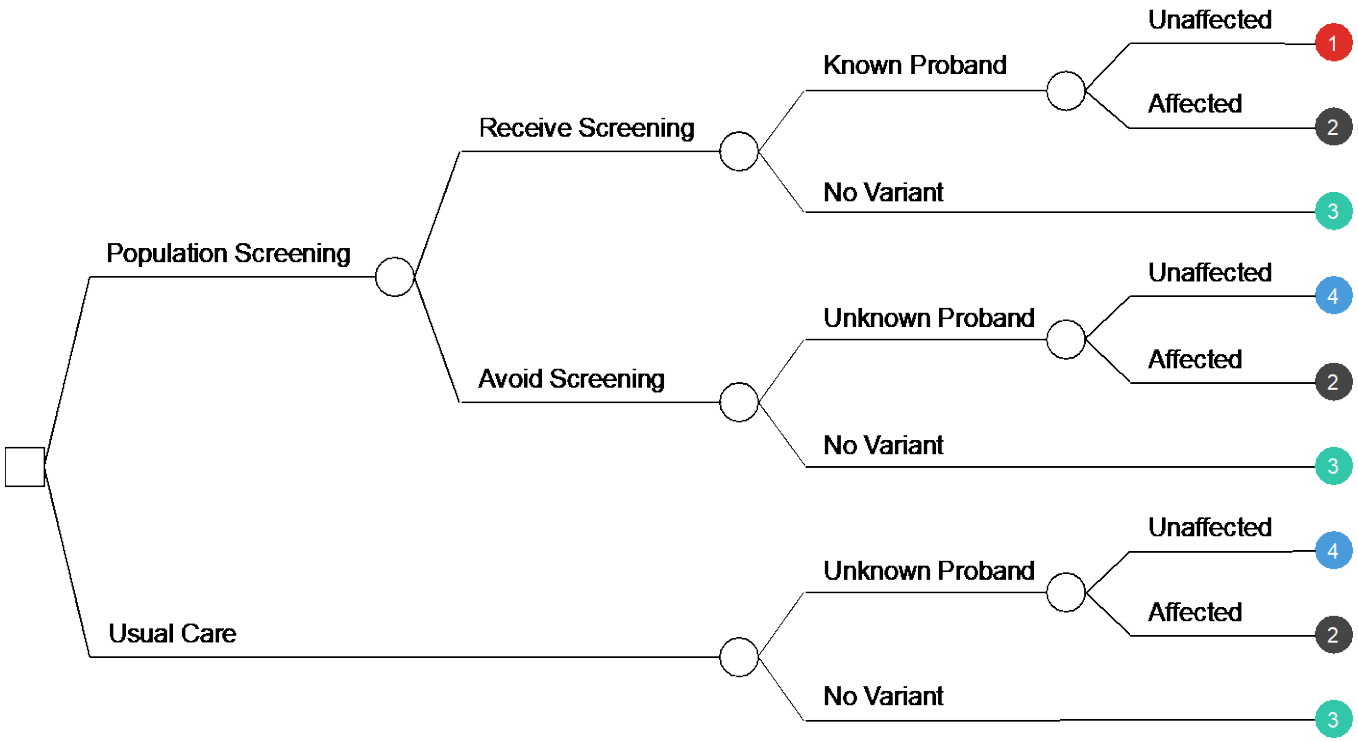
Grzymski, unpublished data Dec 2022.

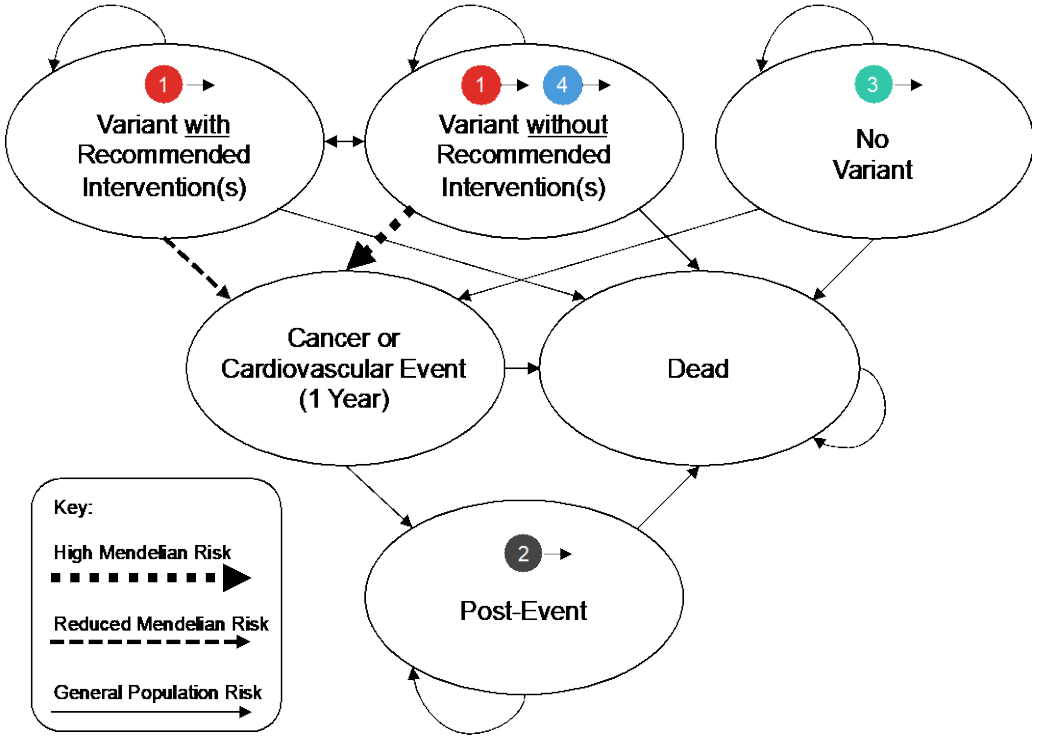
Selected Assumptions

Parameter	Value
Targeted Next Generation Sequencing (NGS)	$250
Sanger confirmation	$250
Genetic Counseling	
Efficacy of family history stimulated testing for HBOC	17%
Adherence to Surveillance	75%
Efficacy of cascade testing	14%

Tier 1 Model Features

Tier 1 Screen vs Family History stimulated testing → **Previously identified?** → **Already affected?** → **Surveillance** → **Clinical outcomes**





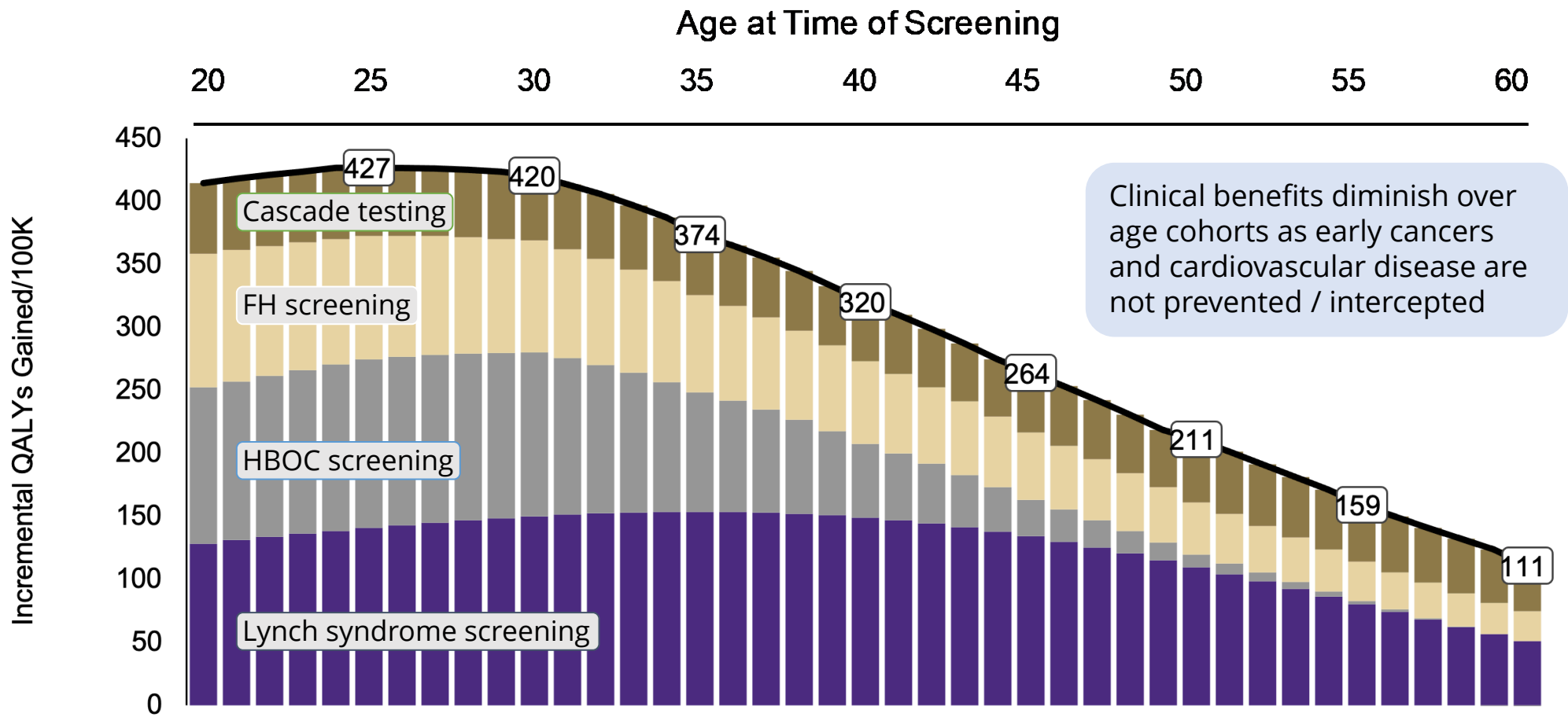
Individual model results

✓ cost-effective
✗ not cost-effective

Model	30 years old	50 years old
HBOC*	$87,700/QALY ✓	$482,100/QALY ✗
LS	$132,200/QALY ✗	$140,400/QALY ✗
FH	$206,700/QALY ✗	$463,500/QALY ✗

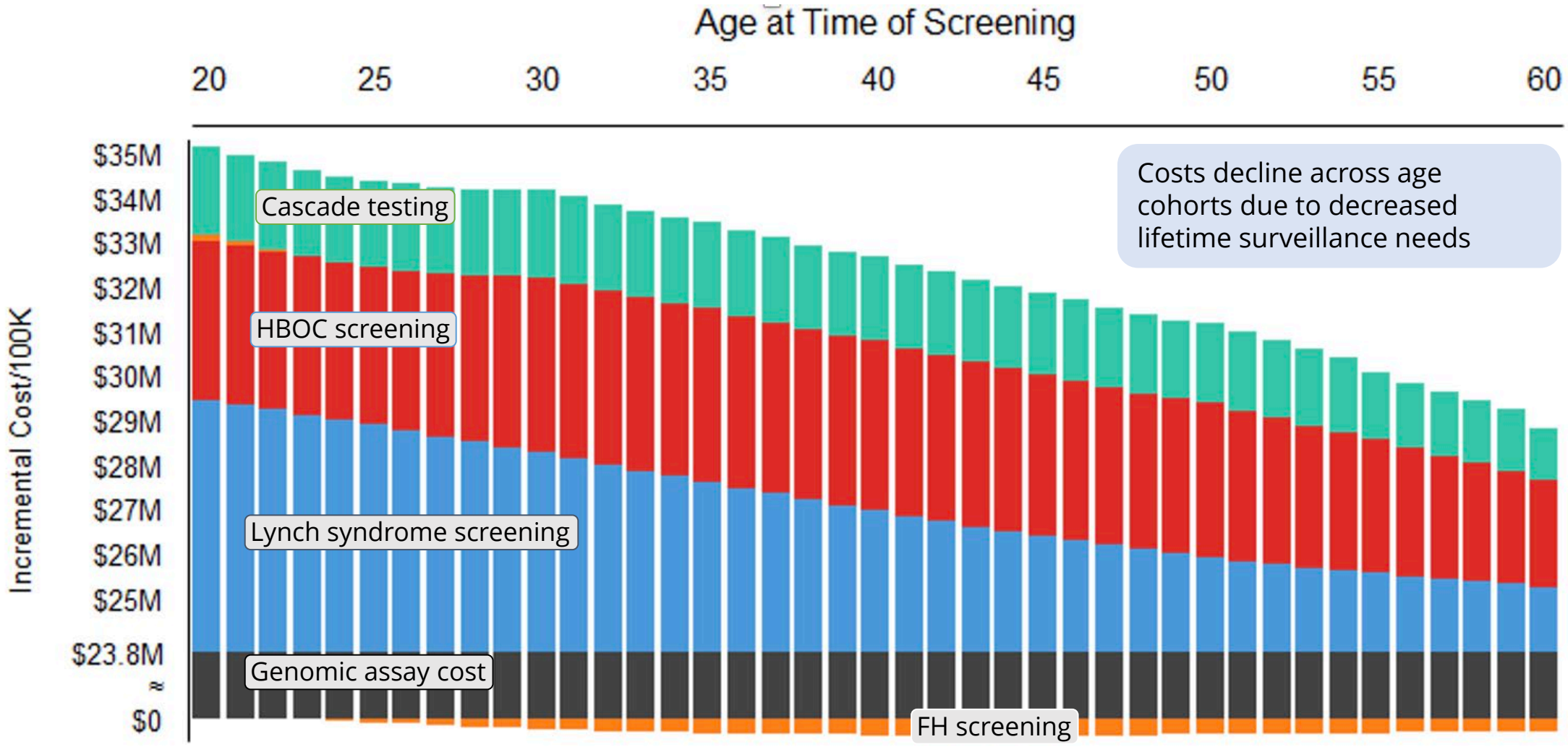
*females

Combined results:
Incremental QALYs per 100,000 screened



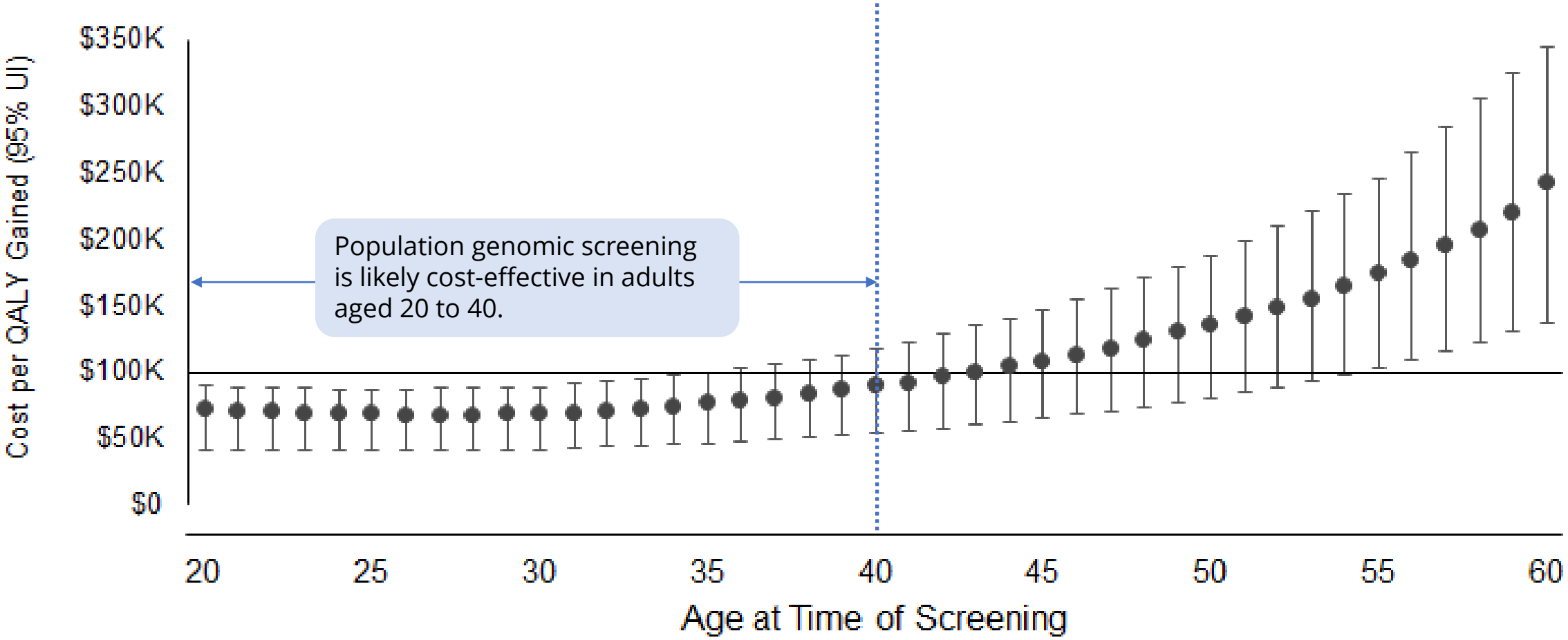
Guzauskas et al, Annals Int Med, May 2023

Combined results:
Incremental cost per 100,000 screened



Guzauskas et al, Annals Int Med, May 2023

Cost effectiveness



Guzauskas et al, Annals Int Med, May 2023

But what if…

Table 3. Base-Case and Scenario Analysis Results

Scenarios for Screened 30-Year-Old Persons	Scenario Inputs					Results per 100 000 30-Year-Old Persons			
	Assay Cost, $	Follow-up Multiplier	Cascade Testing Uptake, %*	Prior Knowledge of Variant, %†	Total Variant Proportion, %‡	Incremental Cost (95% UI), $ *(millions)*	Incremental QALYs (95% UI)	ICER (95% UI), *$/QALY*	Cost-Effectiveness Probability, %§
Main (base-case) analysis	250	1	14	9	1.5	33.9 (27.0–41.1)	495 (401–757)	68 600 (41 800–88 900)	99.4
Societal perspective	250	1	14	9	1.5	25.6 (16.4–40.3)	495 (401–757)	51 700 (24 200–106 200)	99.9
Lower genetic assay cost	100	1	14	9	1.5	19.6 (15.1–24.4)	495 (401–757)	39 700 (23 500–51 800)	100
Higher genetic assay cost	500	1	14	9	1.5	57.8 (45.3–70.7)	495 (401–757)	116 800 (71 200–154 000)	44
Lower adherence to follow-up	250	0.5	14	9	1.5	31.2 (24.9–37.7)	292 (228–436)	106 800 (66 700–141 700)	57
Higher adherence to follow-up	250	1.2	14	9	1.5	35.0 (28.0–42.1)	570 (461–883)	61 400 (37 000–77 900)	100
Without cascade testing	250	1	0	9	1.5	32.0 (25.2–39.0)	436 (347–692)	73 300 (42 000–96 100)	98
Higher uptake of cascade testing	250	1	35	9	1.5	36.9 (29.3–44.7)	582 (478–865)	63 400 (41 100–79 700)	100
Low prior knowledge	250	1	14	7	1.5	34.5 (27.1–41.7)	512 (413–780)	67 400 (40 700–88 000)	99.4
High prior knowledge	250	1	14	11	1.5	33.4 (26.1–40.4)	477 (386–739)	69 900 (41 300–93 000)	98.9
Low variant prevalence	250	1	14	9	1.1	31.4 (24.6–37.9)	371 (303–576)	84 600 (50 800–108 100)	93
High variant prevalence	250	1	14	9	2.0	36.5 (29.1–44.2)	618 (501–945)	59 000 (35 900–75 400)	100

False reassurance

Potential Harm Related to False Reassurance

Under the assumption that 10% of 30-year-olds without a variant subsequently avoid routine disease screening because of receipt of a negative genomic screening result, a loss of 0.05 QALY in this population would lead to genomic screening having no incremental health benefit.

Implication #1

Prevalence drives economic value

- Include the most prevalent conditions
- Combine conditions

Implication #2

Clinical action is required for ‘traditional’ economic value

- Focus on clinical actionability for building value story and driving reimbursement

Implication #3

Screening should be efficient and relatively inexpensive

- Public or private sector reimbursement?
- Delivery and education

Newborn screening

- Large number of rare conditions
- Actionability variable
- Different policy context

Cost-effectiveness of newborn screening

Universal Screening for Rare Newborn Genetic Conditions: Establishing Cost-Effectiveness Before Implementation

iHEA 2007 6th World Congress: Explorations in Health Economics Paper

Posted: 17 Jun 2007

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Date Written: June 15, 2007

Cost-effectiveness of newborn genomic screening

Progress in expanding newborn screening in the United States

To the Editor: We read with interest the recent article by Kingsmore et al., who suggest that universal newborn rapid whole-genome sequencing is attractive for "comprehensive" newborn screening (NBS).[1] Existing US NBS programs are based on mandated routine testing of newborns; evidence-based decision-making processes exist for this testing.[2] Whether policy makers also consider routine rapid whole-genome sequencing of newborns to be warranted may depend on the resolution of a number of evidentiary, ethical, legal, social, and economic

The authors cite two sources of information for this statement: a 2020 publication by Sontag et al.[6] that was the product of a collaboration between CDC and NewSTEPs, a program of the Association of Public Health Laboratories, and a 2008 CDC publication.[7] Sontag et al. used state-based prevalence data from 2015 to 2017 to derive a minimum estimate of the total number of infants with RUSP core conditions expected to be detected through screening of DBS specimens in 2018, i.e., 6,646 infants. Additionally, Sontag et al. cited a model-based prevalence estimate of 6,439 infants detected with RUSP conditions through DBS testing in 2006.[7]

First, we wish to clarify that the RUSP is not restricted to conditions that are screened on the basis of DBS specimens. Currently, the RUSP includes two conditions that

The American Journal of Human Genetics *110*, 1015–1016, June 1, 2023

Cost-effectiveness of newborn genomic screening

Universal newborn genetic screening for pediatric cancer predisposition syndromes: model-based insights

Jennifer M. Yeh[1,2]✉, Natasha K. Stout[1,3], Aeysha Chaudhry[2], Kurt D. Christensen[1,3], Michael Gooch[3], Pamela M. McMahon[3], Grace O'Brien[2], Narmeen Rehman[3], Carrie L. Blout Zawatsky[4], Robert C. Green[1,4], Christine Y. Lu[1,3], Heidi L. Rehm[1,5], Marc S. Williams[6], Lisa Diller[1,7,8] and Ann Chen Wu[1,3,8]

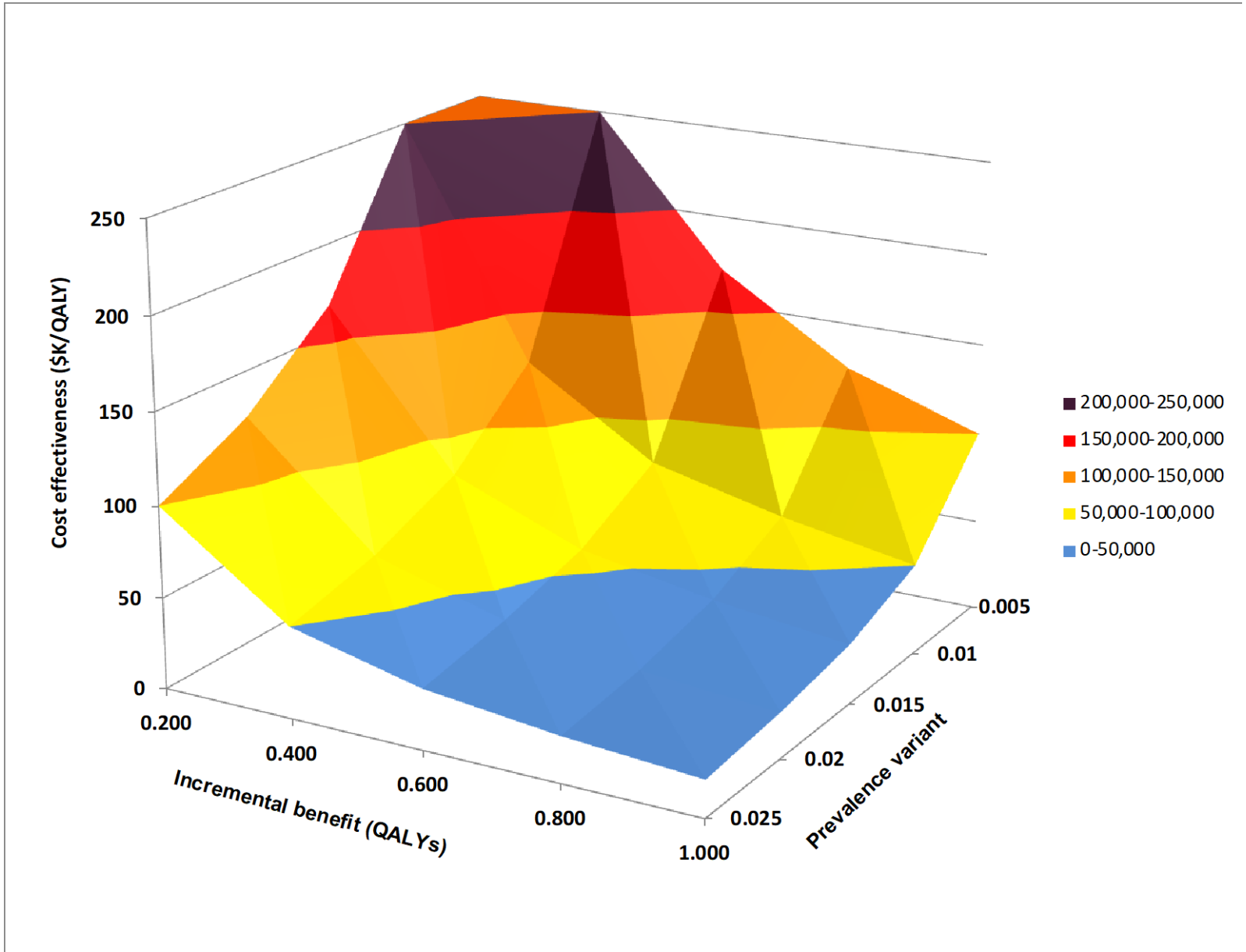
PURPOSE: Genetic testing for pediatric cancer predisposition syndromes (CPS) could augment newborn screening programs, but with uncertain benefits and costs.
METHODS: We developed a simulation model to evaluate universal screening for a CPS panel. Cohorts of US newborns were simulated under universal screening versus usual care. Using data from clinical studies, ClinVar, and gnomAD, the presence of pathogenic/likely pathogenic (P/LP) variants in *RET*, *RB1*, *TP53*, *DICER1*, *SUFU*, *PTCH1*, *SMARCB1*, *WT1*, *APC*, *ALK*, and *PHOX2B* were assigned at birth. Newborns with identified variants underwent guideline surveillance. Survival benefit was modeled via reductions in advanced disease, cancer deaths, and treatment-related late mortality, assuming 100% adherence.
RESULTS: Among 3.7 million newborns, under usual care, 1,803 developed a CPS malignancy before age 20. With universal screening, 13.3% were identified at birth as at-risk due to P/LP variant detection and underwent surveillance, resulting in a 53.5% decrease in cancer deaths in P/LP heterozygotes and a 7.8% decrease among the entire cohort before age 20. Given a test cost of $55, universal screening cost $244,860 per life-year gained; with a $20 test, the cost fell to $99,430 per life-year gained.
CONCLUSION: Population-based genetic testing of newborns may reduce mortality associated with pediatric cancers and could be cost-effective as sequencing costs decline.

Genetics in Medicine (2021) 23:1366–1371; https://doi.org/10.1038/s41436-021-01124-x

Polygenic risk scores

- Prevalence of ‘high-risk’ is greater than monogenic conditions
- Lifetime risk lower
- Multiple conditions

Tier-1 cost-effectiveness ‘landscape’



PRS vs. Tier-1

- Prevalence ~10-20x higher
- Effect size
  - HBOC: ~50% absolute risk reduction with prophylactic surgery
  - PRS: 20-30x lower!
- PRS: Prevalence ~20%, Benefit ~0.03 QALYs
- Cost effectiveness likely above threshold of $100K/QALY (not cost effective)

Genetics in Medicine (2022) 24, 1604–1617

ELSEVIER

Genetics in Medicine

www.journals.elsevier.com/genetics-in-medicine

SYSTEMATIC REVIEW

Can polygenic risk scores contribute to cost-effective cancer screening? A systematic review

Padraig Dixon[1,2,*], Edna Keeney[3], Jenny C. Taylor[4,5], Sarah Wordsworth[6,7], Richard M. Martin[2,3]

- Only 10 studies
- Mixed results
- Some studies modeled less screening in low risk patients

Multi-cancer early detection (MCED)

- Detection/diagnosis, not risk prediction
- Many cancers
- Repeated tests
- Induced health care actions

PharmacoEconomics (2022) 40:1107–1117
https://doi.org/10.1007/s40273-022-01181-3

ORIGINAL RESEARCH ARTICLE

The Potential Value-Based Price of a Multi-Cancer Early Detection Genomic Blood Test to Complement Current Single Cancer Screening in the USA

Ali Tafazzoli[1,5] · Scott D. Ramsey[2] · Alissa Shaul[3] · Ameya Chavan[3] · Weicheng Ye[3] · Anuraag R. Kansal[1] · Josh Ofman[1] · A. Mark Fendrick[4]

- 19 solid cancers
- Estimated cost effective at ~$1100/test

OXFORD

JNCI J Natl Cancer Inst (2022) 114(3): djab168

doi: 10.1093/jnci/djab168
First published online August 27, 2021
Commentary

Multicancer Early Detection: Learning From the Past to Meet the Future

Ruth Etzioni, PhD,[1,2,*] Roman Gulati, MS,[1] Noel S. Weiss, MD, DrPH[1,3]

[1]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [2]Center for Early Detection Advanced Research, Knight Cancer Institute, Portland, OR, USA, and [3]Department of Epidemiology, University of Washington, Seattle, WA, USA

- 3 critical factors:
    1. ability to readily confirm a cancer signal,
    2. the population testing strategy,
    3. the natural histories of the targeted cancers
- "critical gaps in our current knowledge about each factor prevent reliably projecting the expected clinical impact of MCED testing at this point in time"

Summary

- Population screening for CDC Tier-1 conditions provides an excellent model for population genomic screening
- CDC Tier-1 screening likely has beneficial risk-benefit profile and provides good economic value, but:
  - Need further clarity on behavior of those with and without a variant
  - Evidence on all aspects in underserved populations, diverse ancestries
  - Implementation outcomes
- Combining conditions is essential for economic value, but restricting to those with good clinical or patient-centered value is critical
- Genomic population screening applications will vary dramatically in their economic value and evidence requirements

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The Comparative Health Outcomes, Policy, & Economics (CHOICE) Institute

Geisinger

RISE
RATIONAL INTEGRATION OF CLINICAL SEQUENCING

- Funded by NHGRI, R01 HG009694

UNIVERSITY *of* WASHINGTON

Table 1. Selected Input Values, Ranges, and Probability Distributions for the RISE Tier 1 Genomic Screening Model

Input	Base Case	Plausible Range*	PSA Distribution	Source
Variant prevalence, %				
HBOC	0.72	0.54–0.90	Beta	Healthy Nevada Project (21)†
LS	0.35	0.26–0.44	Beta	Healthy Nevada Project (21)†
FH	0.43	0.32–0.54	Beta	Healthy Nevada Project (21)†
Risk-reducing intervention uptake				
HBOC				
Relative mortality reduction: early- vs. late-stage breast cancer	0.94	0.90–1.00	Log-normal	Derived from Zhang et al, 2019 (9)‡
Cumulative mastectomy by age 30 y, %	15	11–19	Beta	Chai et al, 2014 (34)
Cumulative mastectomy by age 40 y, %	30	23–38	Beta	Chai et al, 2014 (34)
Cumulative mastectomy by age 50 y, %	36	27–45	Beta	Chai et al, 2014 (34)
Cumulative mastectomy by age 60 y, %	36	27–45	Beta	Chai et al, 2014 (34)
Cumulative salpingo-oophorectomy by age 30 y, %	8	6–10	Beta	Chai et al, 2014 (34)
Cumulative salpingo-oophorectomy by age 40 y, %	48	36–60	Beta	Chai et al, 2014 (34)
Cumulative salpingo-oophorectomy by age 50 y, %	68	51–85	Beta	Chai et al, 2014 (34)
Cumulative salpingo-oophorectomy by age 60 y, %	74	56–93	Beta	Chai et al, 2014 (34)
LS				
Increased colonoscopy surveillance, ages 20–75 y, %	80	60–100	Beta	Palomaki et al, 2009 (36)
FH				
Proportion of tested persons who take statins, %	60	45–75	Beta	Galper et al, 2015 (52)
Quality of life				
HBOC				
Utility: breast cancer, year 1	0.66	0.50–0.83	Beta	Peasgood et al, 2010 (50)
Utility: ovarian cancer, year 1	0.63	0.47–0.79	Beta	Manchanda et al, 2018 (22)
Utility: post-breast cancer	0.81	0.61–1.00	Beta	Manchanda et al, 2018 (22)
Utility: post-ovarian cancer	0.72	0.54–0.90	Beta	Havrilesky et al, 2009 (49)
Disutility (1-year): mastectomy	0.03	0.02–0.04	Beta	Li et al, 2017 (51)
Disutility (1-year): oophorectomy	0.03	0.02–0.04	Beta	Li et al, 2017 (51)
LS				
Disutility: CRC stage A–C, year 1	0.05	0.01–0.09	Beta	Djalalov et al, 2014 (48)
Disutility: CRC stage D, year 1	0.24	0.14–0.25	Beta	Djalalov et al, 2014 (48)
Disutility: CRC stage D, year 2 and beyond	0.20	0.15–0.25	Beta	Djalalov et al, 2014 (48)
FH				
Utility: MI, year 1	0.87	0.65–1.00	Beta	Galper et al, 2015 (52)
Utility: stroke, year 1	0.33	0.25–0.39	Beta	Gandra et al, 2016 (53)
Utility: post-MI	0.74	0.56–0.93	Beta	Lin et al, 2015 (54)
Utility: poststroke	0.70	0.53–0.88	Beta	Lin et al, 2015 (54)
Selected costs, $				
Screening assay	250	188–313	Normal	Assumption (38, 39)
Follow-up	250	188–313	Normal	Assumption
Mastectomy	22 110	16 583–27 638	Normal	Sun et al, 2019 (43)
Salpingo-oophorectomy	8476	6357–10 595	Normal	Sun et al, 2019 (43)
Mammography	228	171–285	Normal	Sun et al, 2019 (43)
MRI	1403	1052–1754	Normal	Sun et al, 2019 (43)
CRC colonoscopy surveillance (annual)	1555	1166–1944	Normal	Dinh et al, 2013 (20)
Statins (annual)	312	234–390	Normal	Pandya et al, 2015 (47)