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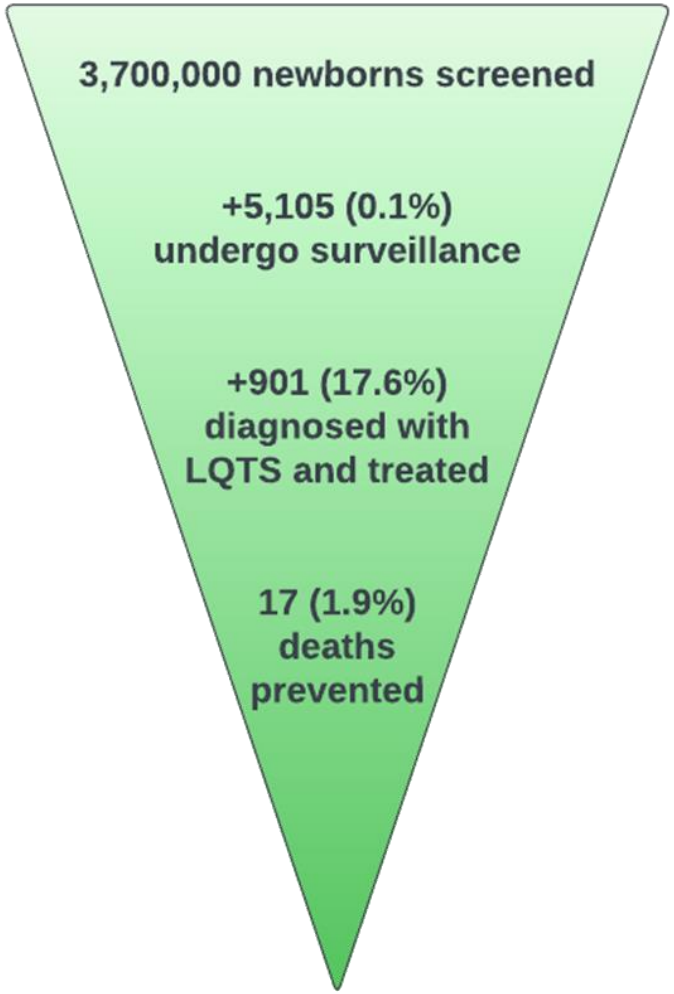
Cost Effectiveness of Newborn Genetic Screening for Long QT Syndrome



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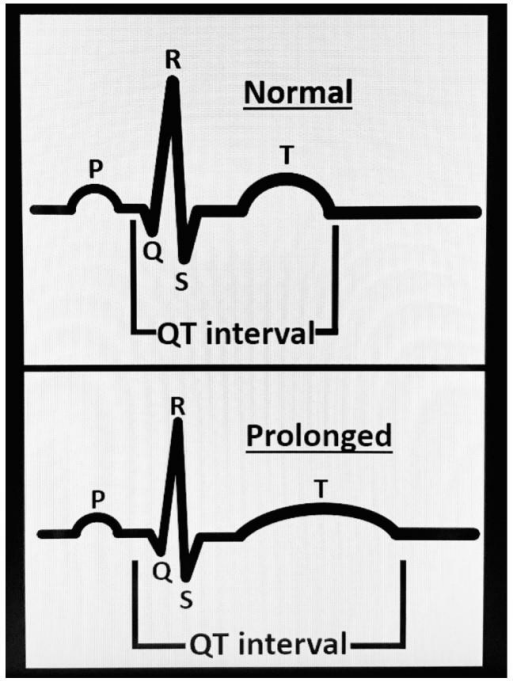
- The authors report no financial interests to disclose

Although rare, long QT syndrome is a leading cause of sudden cardiac death in the young

- Affects between 1 in 2,500 to 1 in 10,000 people
- 15% to 20% of unexplained sudden cardiac death in youth
- 3 genes definitively associated with congenital cases
  - *KCNQ1, KCNH2, SCN5A*



(Semsarian, 2015; Srinivasan, AER, 2018' Wilde, Heart, 2022)

Newborn genetic screening for LQTS is feasible. What's the tradeoff of benefits to harms, costs?

- Opportunistic genetic screening for LQTS is already happening

Genetics inMedicine

www.nature.com/gim

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ACMG STATEMENT

Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG)

David T. Miller[1], Kristy Lee[2], Adam S. Gordon[3], Laura M. Amendola[4], Kathy Adelman[5], Sherri J. Bale[6], Wendy K. Chung[7], Michael H. Gollob[8], Steven M. Harrison[9], Gail E. Herman[10], Ray E. Hershberger[11], Teri E. Klein[12], Kent McKelvey[13], C. Sue Richards[14], Christopher N. Vlangos[15], Douglas R. Stewart[16], Michael S. Watson[17], Christa Lese Martin[18] and ACMG Secondary Findings Working Group[19]*

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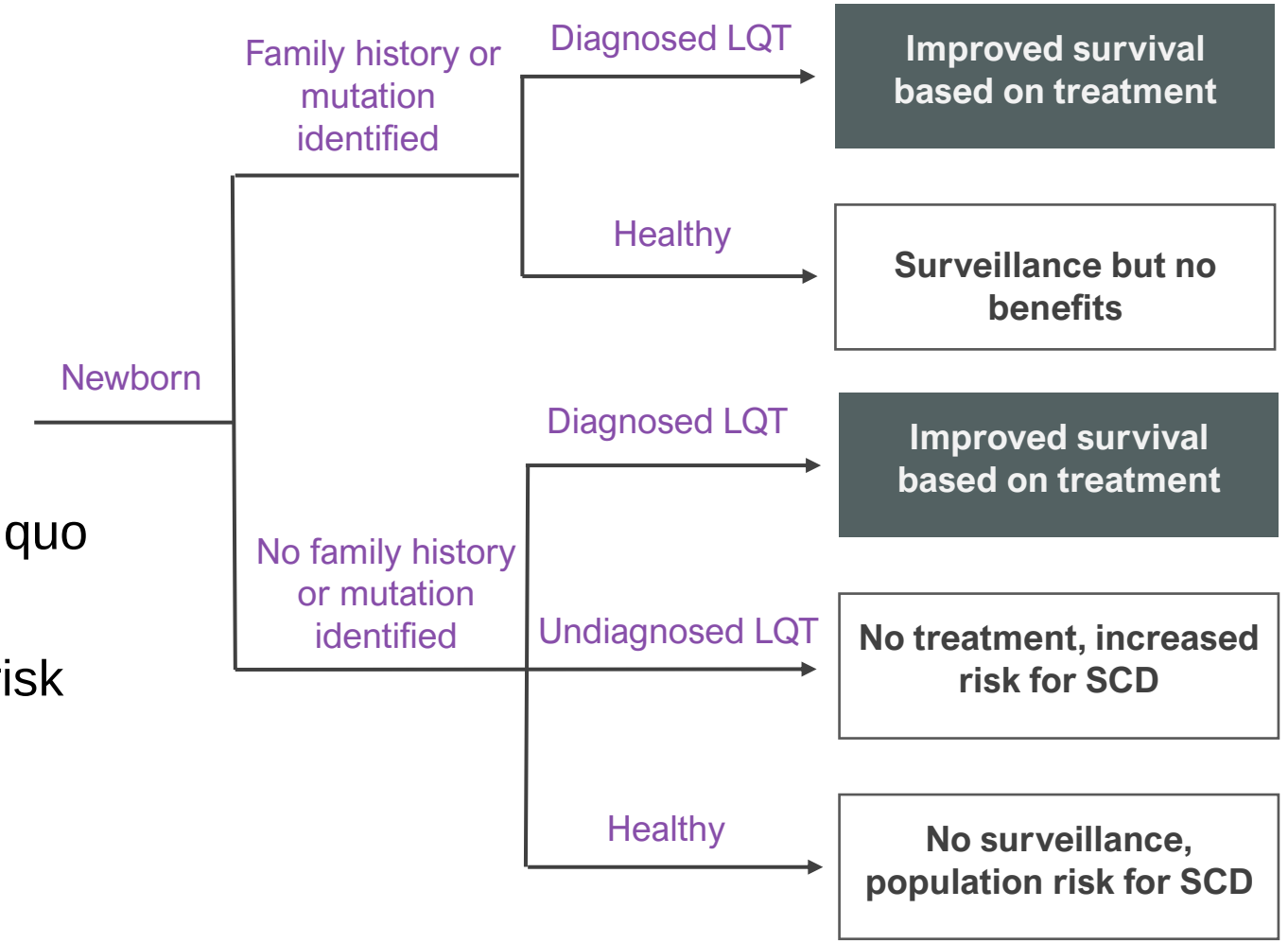
PreEMPT Model: diagnostic testing would be triggered by knowledge of mutation or family history

Approach

- Microsimulation (500 simulations):
  - 40M individuals, standardized estimates to US birth cohort of 3.7M
  - Time horizon: lifetime
- Comparators: universal screening vs status quo
- Treatment: Beta blockers w. possible implantable cardioverter defibrillator if high risk



Key model assumptions included 8 undiagnosed children for every 1 diagnosed child

Parameter	Estimate
Cost of screening/newborn	$15 ($5/gene)
p(D+), diagnosed, age 20	1/20000
Ratio, undiagnosed to diagnosed	8:1
p(M+|D+)	0.80
p(M+|D-)	0.000662
p(SCD)	By Age
SCD reduction from treatment	30%-48%, by gene
P(ICD|moderate/high risk)	2.5%/7.5%

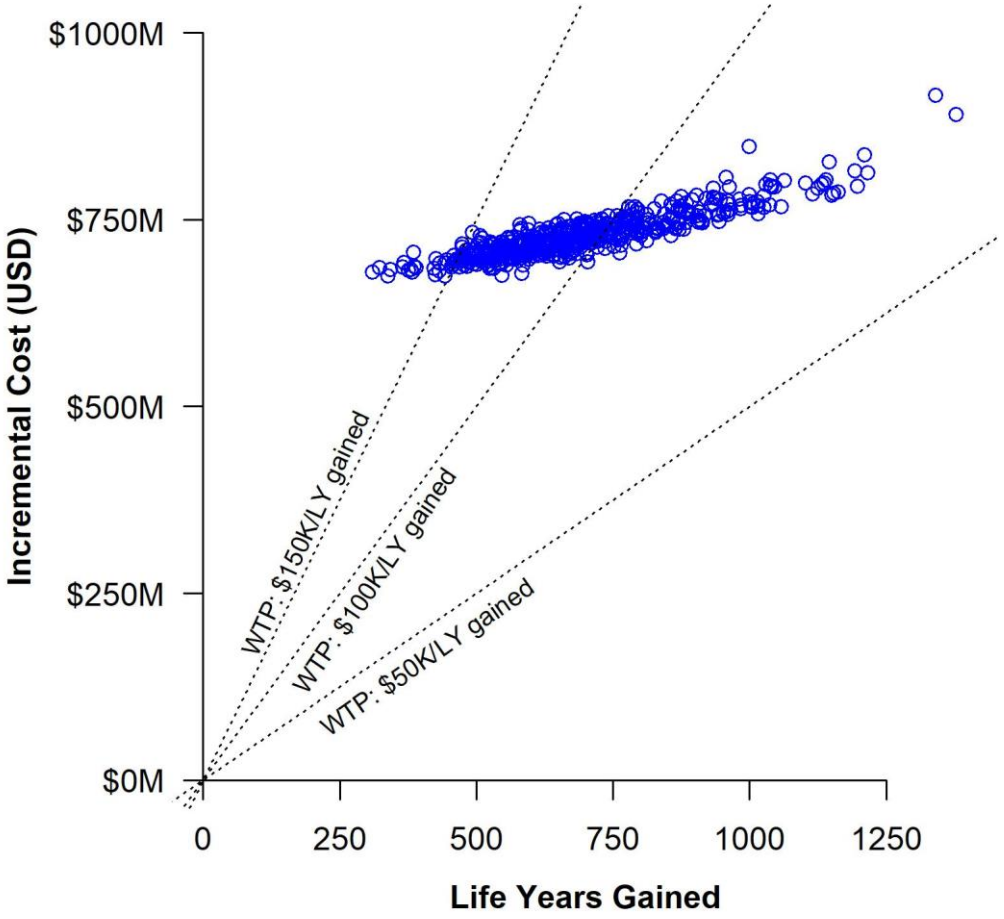
Results: Newborn genetic screening was expected to reduce LQTS deaths by age 20 by 20%

Scenario	Individuals under surveillance	LQTS Cases	% Undiagnosed Long QT	Long QT deaths, age 20	ICDs placed
Usual care	194 (66 to 379)	1,698 (603 to 3,685)	88.9% (86.2%, to 91.0%)	83 (75 to 90)	13 (3 to 33)
Screen all	5,299 (4,609 to 6,100)	1,698 (603 to 3,685)	35.6% (33.3%, to 38.4%)	66 (57 to 73)	78 (21 to 191)
Difference	5,105 (4,406 to 5,838)	NA	-53.1% (-57.2% to -62.3%)	-17 (-13 to -21)	64 (17 to 159)

Population newborn genetic screening for LQTS would cost $105,000 per life year gained

Scenario	Total Cost	Total Life Years	ICER
Usual care	1.7M USD (0.7M to 3.5M)	113,069K (113,064K to 113,073K)	
Screen all	74.6M USD (69.4M to 83.2M)	113,070K (113,066K to 113,074K)	
Difference	**+72.9M USD** **(68.5M to 79.8M)**	**+693** **(423 to 1132)**	**$105,000** **($70,000 to $164,000)**

Model estimates showed large uncertainty in the value of population screening



WTP Threshold (USD per life year gained)	% of Simulations Cost-Effective
$50,000	0%
$100,000	34.6%
$150,000	94.4%

Cost-effectiveness estimates were most sensitive to

- Diagnostic criteria (eg, suspected D+): ICER=$268,000/LYG
- Genetic screening costs
- Surveillance and treatment costs
- Ratio of diagnosed to undiagnosed cases

Newborn genetic screening for LQTS would save lives, but greatly increase the number of children receiving surveillance

- Cost-effective at higher thresholds
- Large uncertainty in estimates
- Improving model to better address benefits in adulthood, cascade screening better; address diversity

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