When Is Precision Public Health Cost Effective?

Health Services and Economics Research

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Precision Public Health & Genomics

- Population-level activities aimed at incorporating novel methods and data systems to improve population health
  - "using the best available data to target more effectively and efficiently interventions of all kinds to those most in need" (Horton, Lancet 2018)
- Applications of genomic technologies in precision public health
  - Screening and diagnosis of rare diseases
  - Screening and preventive interventions for hereditary cancer syndromes
    - Use of family health histories with genetic counseling
    - Cascade testing for familial variants starting with first-degree relatives
  - Pathogen genomics to monitor and curb infectious disease

Genetic Testing to Screen for Genetic Disease

- Genetic testing
  - Cytogenetic (chromosomal) testing – karyotyping, copy number variant microarrays
  - Biochemical genetic testing for gene products (proteins)
  - Molecular testing for DNA sequences and variants
    - Sequencing refers to identifying the order of base pairs in DNA
      - One can sequence individual genes, panels of related genes, or an individual's whole genome or exome
      - In hereditary cancer testing, it was formerly common to sequence just one or two genes, but more common now to sequence panels of genes
- In population screening, sequential testing strategies may include sequencing used as final tier of testing

Tier 1 Evidence-Based Genomic Applications

- **Hereditary breast and ovarian cancer (HBOC)**
  - **Refer for genetic counseling women at risk for *BRCA1* or *BRCA2* variants based on ancestry or personal or family cancer histories**
- **Lynch syndrome (LS)**
  - **Universal tumor testing in new CRC cases followed by germline gene sequencing and cascade testing of relatives of probands**
- **Familial hypercholesterolemia (FH)**
  - **Cascade cholesterol testing for relatives of persons with FH to identify unknown cases of FH**
- **Hereditary hemochromatosis (HH)**
  - **Cascade testing of family members of people who are *HFE* gene p.C282Y homozygotes**

Beyond Tier 1: Molecular Genetic Screening

- Most individuals with Tier 1-associated conditions have not been identified, resulting in limited public health benefits
- Might direct genetic screening be justified? (Khoury & Dotson 2021)
- "Much of the health services and economic research needed to address the DNA-based screening issues are yet to be done." (Murray et al. 2021)

From genes to public health: are we ready for DNA-based population screening? - PubMed (nih.gov)

DNA-based screening and population health: a points to consider statement for programs and sponsoring organizations from the American College of Medical Genetics and Genomics (ACMG) | Genetics in Medicine (nature.com)

Health Economics and Health Services Research

- **Analyses of costs**
  - Costs of care associated with conditions
  - Productivity costs
  - Costs of interventions or programs
- **Outcomes research**
  - Impacts of interventions on health outcomes
  - Quality of life, family spillovers
  - Assessing preferences and values
- **Economic evaluations**
  - Balance between costs and outcomes of policies, programs, or interventions
  - Comparisons of strategies

Economic Evaluation in Health

- Objective: assess relative value of alternative (competing) strategies
  - Value: favorable balance between expected gain in important health outcomes and increase in costs
- Strategies to be compared should each specify
  - Interventions, e.g., drugs and diagnostic tests
  - Target population(s) to whom intervention is offered
  - Implementation protocols
- Balance of costs and outcomes depends on which strategies are compared
  - A strategy may appear cost-effective compared to current practice or "doing nothing" but not relative to a competing strategy

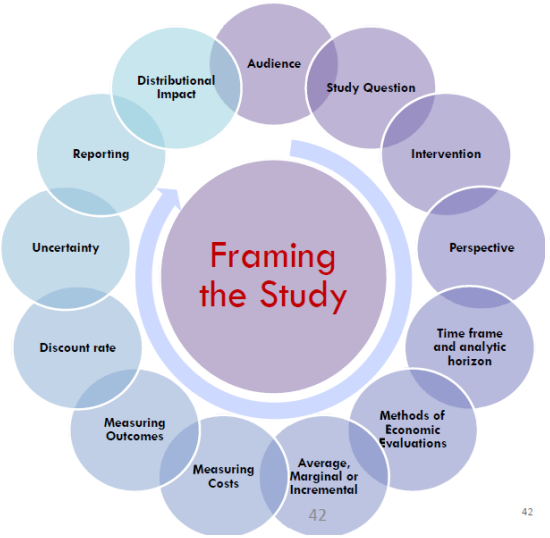
Limited Economic Evaluations

- Cost-consequences analyses
  - Summarize expected costs and outcomes, no common metric
- Cost-minimization analyses (CMA)
  - Which approach yields the lowest cost?
- Budget impact analysis (BIA)
  - Net expenditure for a payer, program, or government
- Cost-effectiveness analysis (CEA)
  - What is the average cost per intermediate outcome, e.g., cost per case identified?
  - Such an analysis doesn't require modeling of health outcomes

Complete Economic Evaluations

- Cost-effectiveness analysis (CEA)
  - Which approach costs less per unit of health outcome gained?
  - A CEA that expresses health outcomes in quality-adjusted life-years (QALYs) can also be called cost-utility analysis (CUA)
    - Incremental cost-effectiveness ratio (ICER), e.g., cost per QALY gained
    - Some CEAs calculate net monetary benefit by multiplying QALYs by presumed willingness to pay for a QALY and subtracting net costs
- Cost-benefit analysis (CBA)
  - Is monetary value of welfare benefits to society greater than total cost?
  - Used to inform regulatory or legislative policies, should be multisectoral, not limited to health sector

Framing a CEA Study



- Study question
- Intended audience(s) and perspective(s) of analysis
  - Healthcare sector or society?
- Strategies to compare
  - Calculate total treatment costs for each strategy
  - Calculate outcomes for each strategy
  - If a strategy costs less and has better outcomes than each alternative, it is "dominant", i.e., "cost-saving"
  - If not, calculate incremental cost-effectiveness ratio (ICER) of unit cost per unit outcome relative to next best strategy

Interpretation of ICERs

- Rules of thumb: Benchmark ICER values
  - A single threshold, such as $50,000 or $100,000 per QALY, or a range, such as $50,000 to $150,000 per QALY
  - In low- and middle-income countries, common practice is to use 1x and 3x gross domestic product per capita
- ICER rules of thumb may not influence decisions by payers
  - Interventions with higher ICERs routinely reimbursed
  - Strategies that are cost-saving may not be funded
  - Value is in the eye of the stakeholder, not the researcher

QALYs and DALYs, Oh My!

- QALYs are the product of years lived in a health state and the multidimensional "utility value" of that state, where 1 is perfect health and 0 is equivalent to death
  - Health state utility values are supposed to represent preferences about tradeoffs
- "Disability-adjusted life-years" (DALYs)
  - Years lived with disability (YLD) is product of years lived in a health state with a "disability weight", where 0 is perfect health and 1 is equivalent to death
- Use of QALYs and DALYs can be controversial

Tier 1 Case Study: Lynch Syndrome (LS)

- Lynch syndrome results from variants (mutations) in genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*) that affect DNA mismatch repair (MMR) system
- Autosomal dominant disorder accounts for 2-5% of colorectal cancer (CRC) and endometrial cancer (EC)
  - *MLH1*, *MSH2* mutations associated with earlier onset
- Cumulative risk of CRC to age 70: 40% in LS vs 4.5% population risk,
  - Risk of CRC 10-22% for *MSH6*, *PMS2* and 58-82% for *MLH1*, *MSH2* mutation carriers (Kastrinos et al. 2021)

Possible Lynch Syndrome Testing Strategies

- Testing of patients with CRC/EC followed by genetic counseling and cascade testing of relatives
  - Targeted tumor testing for patients selected based on age cutoffs, family history, or other criteria
  - Universal testing of newly diagnosed patients with CRC
    - Sequential tumor testing beginning with immunohistochemistry (IHC) and/or microsatellite instability (MSI), followed by other intermediate tests and MMR gene sequencing (Tier 1 recommendation)
    - Direct gene sequencing
- Population germline genetic testing (no cancer)
  - Reporting secondary results from clinical sequencing
  - Population screening

Clinical Utility of Diagnosis of Lynch Syndrome

- Intensive endoscopic surveillance in LS carriers can reduce CRC risk by 60% but is burdensome and risks complications
  - Original US guidelines recommended colonoscopy every 1-2 years beginning at age 20-25 years for individuals with pathogenic variants in any MMR gene associated with LS
  - European and some US guidelines recommend onset of surveillance at 30-35 years for less penetrant *MSH6*, *PMS2*, and *EPCAM* genes (Drogan and Kupfer 2022)
- Other preventive strategies
  - High-dose aspirin in randomized trial shown to reduce risk of CRC in LS carriers by 35-50%
  - Lower-dose aspirin being studied in LS carriers

Is Lynch Syndrome Testing Cost-Effective

- Tumor testing and cascade testing is widely believed to be cost-effective (Di Marco et al. 2018)
  - —However, findings differ based on behavioral assumptions, comparisons of strategies, and definitions of cost-effectiveness (Grosse 2015)
  - —Age-targeted testing (patients with CRC less than 50 years old) less sensitive but most cost-effective
  - —Universal sequential tumor testing likely to be cost-effective compared to age-targeted testing if identification of index patient is followed by cascade testing and intensive surveillance of carriers

Cost of Genetic Counseling and Testing

- Pre-2015 CEAs had broadly similar cost estimates, except Severin et al. assumed cost of gene sequencing 5-7x other studies (Grosse 2015)

Table 3. Base case values of cost assumptions of routine testing for Lynch Syndrome in patients with colorectal cancer (CRC) and first-degree relatives, in 2014 US dollars.

Study	Pre-Test Counseling for CRC Patients	IHC	Post-Test Counseling	Counseling for Gene Sequencing	Gene Sequencing for *MLH1* Gene	Approaching and Counseling Relatives	Test for Known Family Mutation	Combined Cost of Counseling and Testing A Relative
Mvundura *et al.* [32]	22	290	106	194	899	156 * plus 194	61	411
Ladabaum *et al.* [31]	NR	300	112	198	942	118	492	610
Sie *et al.* [34]	25	184	136	0	1184	77	353	430
Snowsill *et al.* [29,35]	0	366	0	103	714	103	265	368
Severin *et al.* [14]	57	166	161	0	5268	57	281	338
Barzi *et al.* [30]	NR	300	112	198	942	118	492	610

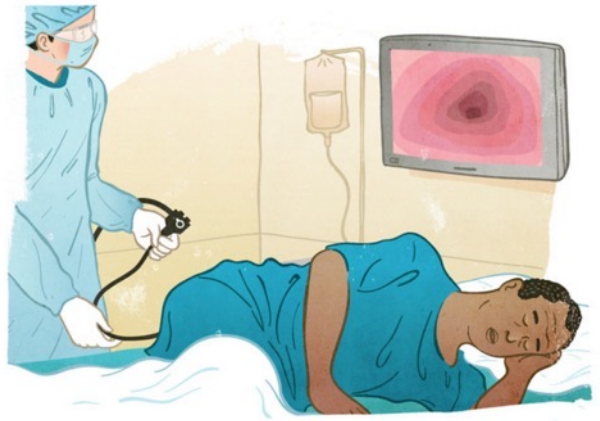
* This cost estimate is based on the CDC model, which adjusted the estimate in the published article for inflation to 2007 dollars. IHC: immunohistochemistry; *MLH1*: mutL homolog 1; NR: Not reported.

Challenges to LS Testing Cost-Effectiveness

- If 2 or more relatives undergo testing for each proband identified, LS tumor testing appears cost-effective (Grosse 2015)
- Uptake of cascade testing is lower in practice
  - Publicly funded BC Cancer Hereditary Cancer Program in British Columbia, Canada found 1.25 relatives tested per HBOC/LS proband (Braley et al. 2021)
  - US laboratory data indicate fewer than 0.5 relatives may be tested per proband in absence of centralized follow-up, even if testing is free (Uson et al. 2022; Stefka et al. 2023)

Other Gaps in Evidence of Clinical Utility

- Evidence is lacking on optimal frequency of endoscopic surveillance (Williams et al. 2023)
  - Lower frequency could reduce costs
- CEA models have assumed ~80% uptake of colonoscopy surveillance in LS carriers, but evidence is sparse.
  - One British registry-based study reported that 25% of LS carriers engaged in endoscopic surveillance, mostly every ~2 years (Newton et al. 2015)

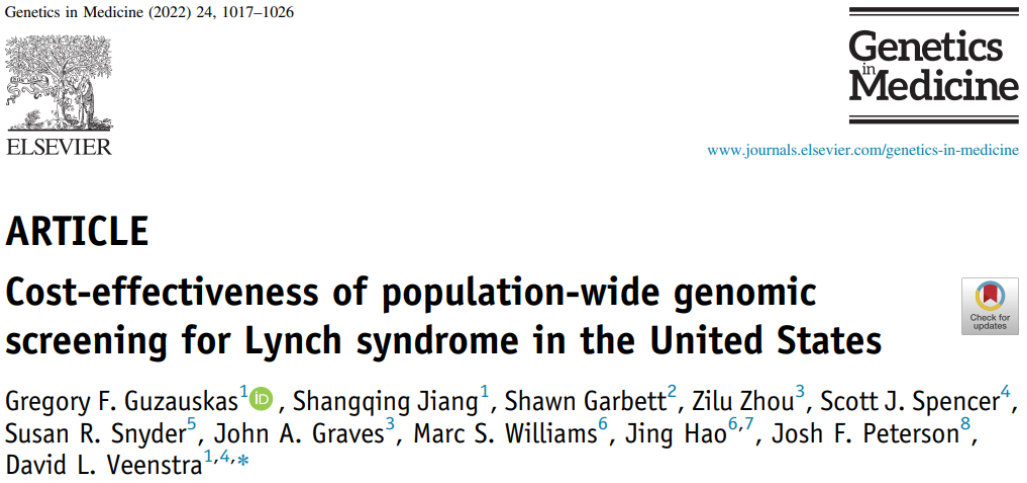


Direct Germline Sequencing of Patients

- Direct genome sequencing of patients in place of reflex IHC/MSI tumor testing has been proposed
  - Can improve LS case detection since many patients drop out from complex sequential tumor testing pathway before undergoing gene sequencing (Gudgeon et al. 2021)
  - Gudgeon et al. suggested that it would be cost neutral to directly refer new patients to gene sequencing if a LS multigene panel cost less than $700
  - Hao et al. (2021) suggested break-even cost of $368 for LS multigene sequencing panel

Population-Based Germline Sequencing

- Genome sequencing of US adults age 30 at usual risk of CRC
  - Guzauskas et al. (2022) modeled sequencing LS gene panel, assuming
    - $200 cost of gene panel
    - 80% uptake of intensive colonoscopy surveillance
    - Potentially cost-effective using $150,000 per QALY rule of thumb



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ARTICLE

Cost-effectiveness of population-wide genomic screening for Lynch syndrome in the United States

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Population-Based Germline Sequencing

- Genome sequencing of US adults
  - Guzauskas et al. (2023) modeled sequencing for LS, HBOC, and FH variants at age 30
    - Gene panel cost of $250
    - Confirmatory cost for probands
    - Modeled low uptake of cascade testing, but high uptake of preventive measures
    - ICER ~$70,000 per QALY

Annals of Internal Medicine ORIGINAL RESEARCH

Population Genomic Screening for Three Common Hereditary Conditions

A Cost-Effectiveness Analysis

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Implications for Genomic Economic Evaluations

- Epidemiology matters
  - Genotypic heterogeneity should be taken into account
- Behaviors matter
  - Uptake of testing by family members and services by carriers can influence impacts on population health
- Comparisons matter
  - Cost-effectiveness is not an innate attribute of a test or intervention, but depends on context and comparators
  - Many ask, “Is intervention X cost-effective?” Better to ask, “When and how might X be cost-effective?”

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