ISPOR issue panel: Capturing family spillover effects

Incorporating Family Members in Economic Evaluation of Genetic Testing

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Senior Scientist at SickKids

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Member, Ontario Health Technology Advisory Committee

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Outline

- Theoretical foundation for economic evaluation
- Gap between theory and recommended practice as per economic evaluation guidelines
- Genetic testing technology
  - Impact on design and conduct of economic evaluation
    - Trio genome and exome sequencing in pediatric rare disease
    - Cascade genetic testing in children with cardiomyopathy
- Need for guidance

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Principles of Welfare Economics

The utility principle

- ***individuals*** rationally maximize their welfare by ordering options and choosing the preferred option

Individual sovereignty

- ***individuals*** are themselves the best – some might say 'the only' – judges of what contributes most to their utility and how much that contribution is.

Individuals are not categorized into different types of consumers, such as patients or caregivers. All are members of society. Ultimate goal remains achieving a net welfare gain in society.

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Extra-welfarism

"Societal welfare"

- Social and health policy go beyond mere judgments of *individual* welfare
- Societal welfare often the focus of policy making because it deliberately aims to consider more than just heath gains in patients

Distribution of health, wealth, resources, access, in a population as a whole also matters

- Equity
- Additional ethical foci relate to needs of special populations, e.g. marginalized, indigenous, rural, children, seniors

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What do the Guidelines Say?

- The decision problem requires specifying a target population that will use and benefit from an intervention
- Guidelines:
  - focus on consumption (use) of an intervention or service and not on who else benefits in society
  - Specifies target population as **patients**
  - Specifies measurement of spillover costs, especially caregiving time, for informal caregivers
  - Allows for measurement of spillover health consequences for informal caregivers, but provides little methodologic guidance

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Spillover Effects

- Caring for a chronically ill child has been associated with reduced QoL and a higher risk of developing anxiety and depression in parents
- Effects can extend to other family members
- Childhood illness is also associated with employment changes and other financial burdens
- Parents and other caregivers can experience a positive utility from caregiving
- Focusing solely on the costs and health consequences of patients alone may underestimate the true burden of many illnesses that have a large family impact
- Spillover effects can be related to costs (time losses, consumption of health services) and health effects

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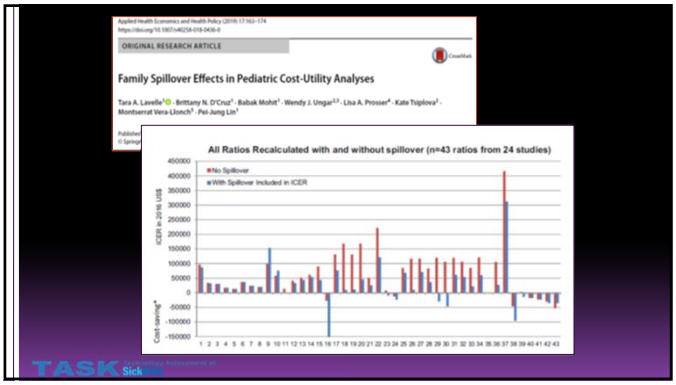

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Findings from Sequencing

- *Primary (diagnostic):*
  - targeted search for variants known to be definitely or likely causally related (pathogenic) to reason for testing
  - Target list and length of list varies by indication
- *Secondary (screening):*
  - American College of Medical Genetics and Genomics (ACMG) SF 3.2 list of >90 medically actionable variants (e.g. *BRCA1,2*, Lynch syndrome, cardiomyopathies)

→ Accuracy and clinical utility of genome sequencing is optimized if sequencing is conduced in **TRIOs**: child proband + biologic parents

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Cost-effectiveness Analysis of Trio ES and Trio GS in Pediatric Rare diseases

Patient Population:
- Ontario children with unexplained disease of suspected genetic origins, often with development delay, multiple congenital anomalies + parents

Study Design:
- Randomized controlled trial of trio ES vs. trio GS

Microcosting:
- Sequencing (NovaSeq 6000) broken down into series of inputs. Volumes of use and price estimated for each input.
- Aggregated cost per ES trio and GS trio assessed across 7 cost categories: Reagents, Consumables, Equipment, Shipping and ordering, Software, Labour, and Overhead.

Effectiveness:
- Proportion of test population with a ≥ 1 positive primary finding = diagnostic yield

Probabilistic analysis:
- Uncertainty captured by specifying input ranges with probability distributions. Data sampled 5,000 times → 95% confidence intervals around cost point estimates.

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Cost by Diagnostic Yield Category

ES Cost per Trio (n=329)			GS Cost per Trio (n=324)		
CAD 2,889 (95% CI 2,568, 3,493)			CAD 4,364 (3,985, 5,014)		
USD 2,140 (95% CI 1,903, 2,588)			USD 3,233 (2,953, 3,715)		
Diagnostic + Partially Diagnostic (n=118, 35.9%)	Potentially Diagnostic (VUS) (n=66, 20.0%)	No + Non-Diagnostic (n=145, 44.1%)	Diagnostic + Partially Diagnostic (n=106, 32.7%)	Potentially Diagnostic (VUS) (n=82, 25.3%)	No + Non-Diagnostic (n=136, 42.0%)
CAD 2,745	CAD 2,756	CAD 2,676	CAD 4,181	CAD 4,209	CAD 4,139
USD 2,033	USD 2,042	USD 1,982	USD 3,098	USD 3,118	USD 3,067
Incremental cost GS vs. ES:		**CAD 1,475 (95% CI 1417, 1521)**		**USD 1,093 (95% CI 1,050, 1,127)**	

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Key Trio Microcosting Findings

- Trio sequencing workflow and microcosts vary by patient population and indication for testing
- Trio sequencing is more costly than standard singleton approaches but can offer more timely results, with fewer health care visits by parents.
- Rapidly evolving knowledge regarding genotype-phenotype links will increase Dx yield, clinical utility and increase value for money
- Not captured:
  - Primary and secondary variants can trigger cascade testing and increase referrals to specialists for family members → increased healthcare costs
  - Increased surveillance and the possibility of averting adverse long-term outcomes and improved life expectancy for patients and family members → increased QALYs

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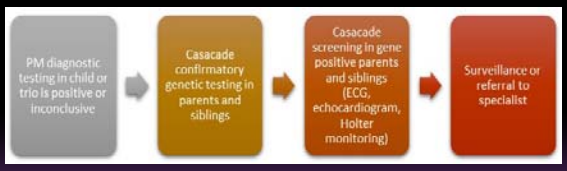
Moving Toward Full Economic Evaluation…

Pediatric cardiomyopathy: Identify genetic variants early to better guide treatment, e.g. implantation of cardioverter defibrillator, to avert sudden cardiac death



Are cascade health services in family members considered spillover effects?

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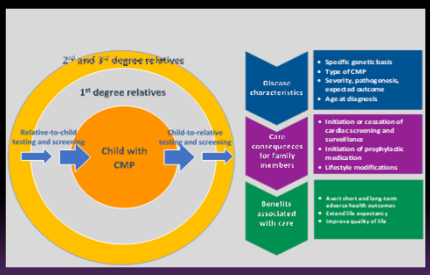
… not if they are part of the target population



Adapted from: Cernat A. *Cascade genetic testing and health service use in families of children with cardiomyopathy: Implications for health technology assessment*. MSc Dissertation, 2020.

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Incorporating Family Members in Genetic Testing Economic Evaluation

- Incorporating cascade costs and health effects of primary and secondary findings into economic models complex but not impossible
  - Utilities for health states → QALYs
  - Utilities for states defined by level of risk → ?
  - Lifetime models
- Model heath risks and outcomes for patients and family members separately
- Model secondary findings from genetic testing as a targeted screening intervention
- Aggregate and determine costs and QALYs per target population rather than individual

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Moving the Guidelines Forward

PharmacoEconomics
https://doi.org/10.1007/s40273-023-01321-3

ORIGINAL RESEARCH ARTICLE

Recommendations for Emerging Good Practice and Future Research in Relation to Family and Caregiver Health Spillovers in Health Economic Evaluations: A Report of the SHEER Task Force

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