ARCC
Canadian Centre
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in Cancer Control

ARCC Program Area Webinar: Dr. Dean Regier

Thursday August 25th, 2016

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Advancing Health Economics, Services, Policy and Ethics

DOES SOCIETAL WILLINGNESS TO PAY HAVE A ROLE IN PRIORITY SETTING? PRECISION MEDICINE AS A CASE STUDY

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25 August 2016
ARCC Webinar

Outline

- Context Willingness to Pay
- Context Precision Medicine
- Context Priority Setting/Public Engagement
- Utility for knowledge (Why not)
- Cost-benefit within an extra-welfarist framework
- Discussion

Willingness to Pay

- Neoclassical economics (aka welfarist)
  - Good are substitutable; preferences reveal ‘worth’ i.e. Utility
  - Individuals maximize utility
  - People act on the basis of full and relevant information
- WTP is the trade-off between marginal utility of additional money and marginal utility for a good

IS WTP RECOMMENDED IN HEALTH ECONOMIC EVALUATION?

Health Econ Evaluation Guidelines

CADTH/NICE Recommend

1. Reference case: cost-utility (ΔC/ΔQALY)
   - *meaningful differences in HRQoL is demonstrated*
2. Reference case: cost-effectiveness (e.g. ΔC/LYG)
   - *when CUA is an inappropriate choice*

- WTP for health gain is required (λ)
  - λ is shadow price (infers: given budget), or social value for health (infers: flexible budget)

CADTH Guidelines for the Economic Evaluation of Health Technologies: Canada, 3rd Edition, 2006.

Economic Evaluation types

3. Reference case: cost-minimisation (ΔC)
   - *patient outcomes....are essentially equivalent*

4. Cost-benefit analysis (WTP-ΔC)
   - *may be useful in some situations, extensive sensitivity analysis*

CADTH Rationale

- CBA limitations w/r/t willingness to pay
  - Methods issues (WTP elicitation)
  - Ethics issues (WTP linked to ability to pay)

- When is CBA appropriate?
  - Quantification using QALYs difficult (e.g., via the EQ-5D)
  - Process outcomes are important (e.g., access; time waiting)

ARTICLE

Oligonucleotide Microarray Analysis of Genomic Imbalance in Children with Mental Retardation

J. M. Friedman, Ágnes Baross, Allen D. Delaney, Adrian Ally, Laura Arbour, Jennifer Asano, Dione K. Bailey, Sarah Barber, Patricia Birch, Mabel Brown-John, Manqiu Cao, Susanna Chan, David L. Charest, Noushin Farnoud, Nicole Fernandes, Stephane Flibotte, Anne Go, William T. Gibson, Robert A. Holt, Steven J. M. Jones, Giulia C. Kennedy, Martin Krzywinski, Sylvie Langlois, Haiyan I. Li, Barbara C. McGillivray, Tarun Nayar, Trevor J. Pugh, Evica Rajcan-Separovic, Jacqueline E. Schein, Angelique Schnerch, Asim Siddiqui, Margot I. Van Allen, Gary Wilson, Siu-Li Yong, Farah Zahir, Patrice Eydoux, and Marco A. Marra

The cause of mental retardation in one-third to one-half of all affected individuals is unknown. Microscopically detectable chromosomal abnormalities are the most frequently recognized cause, but gain or loss of chromosomal segments that are too small to be seen by conventional cytogenetic analysis has been found to be another important cause. Array-based methods offer a practical means of performing a high-resolution survey of the entire genome for submicroscopic copy-number variants. We studied 100 children with idiopathic mental retardation and normal results of standard chromosomal analysis, by use of whole-genome sampling analysis with Affymetrix GeneChip Human Mapping 100K arrays. We found de novo deletions as small as 178 kb in eight cases, de novo duplications as small as 1.1 Mb in two cases, and unsuspected mosaic trisomy 9 in another case. This technology can detect at least twice as many potentially pathogenic de novo copy-number variants as conventional cytogenetic analysis can in people with mental retardation.

Mental retardation (MR) produces life-long disability, and its burden on affected families and society is enormous. Moderate-to-severe MR, which occurs in ~1% of the population,[1,2] is etiologically heterogeneous. Chromosomal abnormalities are the most common recognized cause, accounting for ~10% of MR in most case series,[3,4] but no etiology is recognized in at least one-third to one-

Over the past several years, constitutional gain or loss of genomic segments containing only 1–5 Mb of DNA has been found to be another important cause of MR.[8] These submicroscopic chromosomal alterations are usually diagnosed by locus-specific FISH,[9] a test that provides much higher resolution than that of conventional cytogenetic analysis. However, locus-specific FISH is a labor-intensive

The genomic technology (1)

- Intellectual disability
  - Developmental limitations, life-long disability
  - One-third to half have no diagnosis
- Diagnosis of genetic abnormality
  - Karyotype (half idiopathic)
  - Array genomic hybridization (higher resolution, more individuals have cause established)
- Benefit of establishing a genetic cause
  - Information (Will QALYs work?)
  - EQ-5D domains; length of life not affected

Preference-based utility for knowledge

Which postnatal test would you prefer?

Example Choice	Test A	Test B	Neither
Number of children whose genetic condition is identified with this test	10 children in 100 with DD who are tested	20 children in 100 with DD who are tested	In this scenario, you prefer that the child would NOT be tested
Time waiting for the results of the test	8 weeks	1 week	
Cost to you	$750	$1750	

In which of the following situations would you choose to be tested?

___1) Test A only
___2) Test B only
___3) Neither

Regier DA, Friedman JM, Ryan M, Marra CA. Valuing the benefit of diagnostic testing of idiopathic developmental disability: willingness to pay from families of affected children. Clinical Genetics. 2009; 75(6):514-521.

Preference-based utility estimates

Attribute	Mean	SE
Number of children receiving a diagnosis	16.16**	3.56
Time waiting	-0.03**	0.01
Cost to you (hundreds of $)	-0.123**	0.009
Gender , Testing	-0.98**	0.150
Age, Testing	0.009	0.006
Diagnosis, Testing	0.30**	0.098
Mid income , Testing	0.21**	0.083
High income, Testing	0.005	0.081

Number of draws to simulate posterior: 2,000; Simulated log-likelihood=-863.72; Pseudo R^2 =0.45; **Significant at the 5% level

Marginal WTP	
Additional child in 100 tested receiving a diagnosis	$130.95
One week reduction in waiting time	$24.31
Overall WTP for scenario (10 in 100 tested additional children identified)	
Mean (95% CI)	$1,118 (498 to 1,788)

Aim: What is the cost-benefit of AGH compared to standard care?

Cost

BC Health-care payer perspective

Direct costs were considered

Benefit

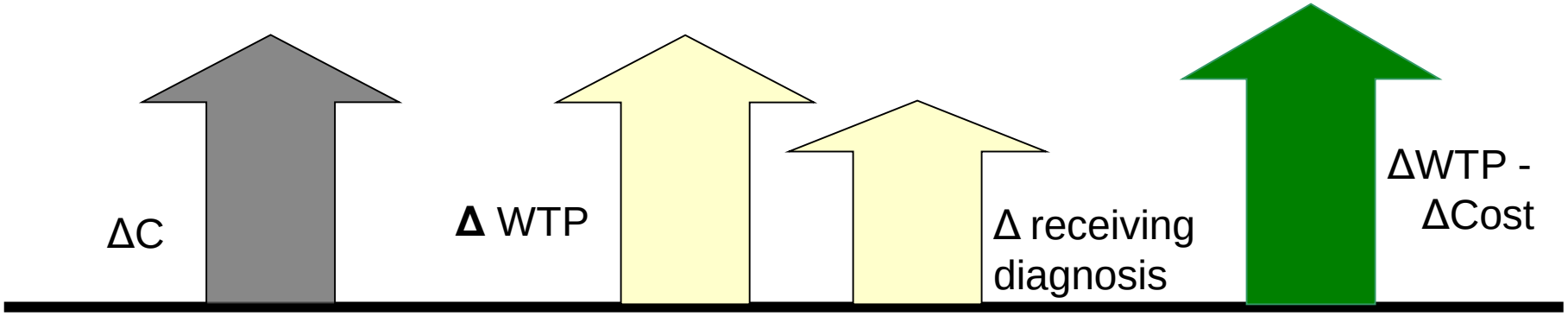
Willingness to pay valued from a DCE

Increase in number of children receiving a genetic diagnosis

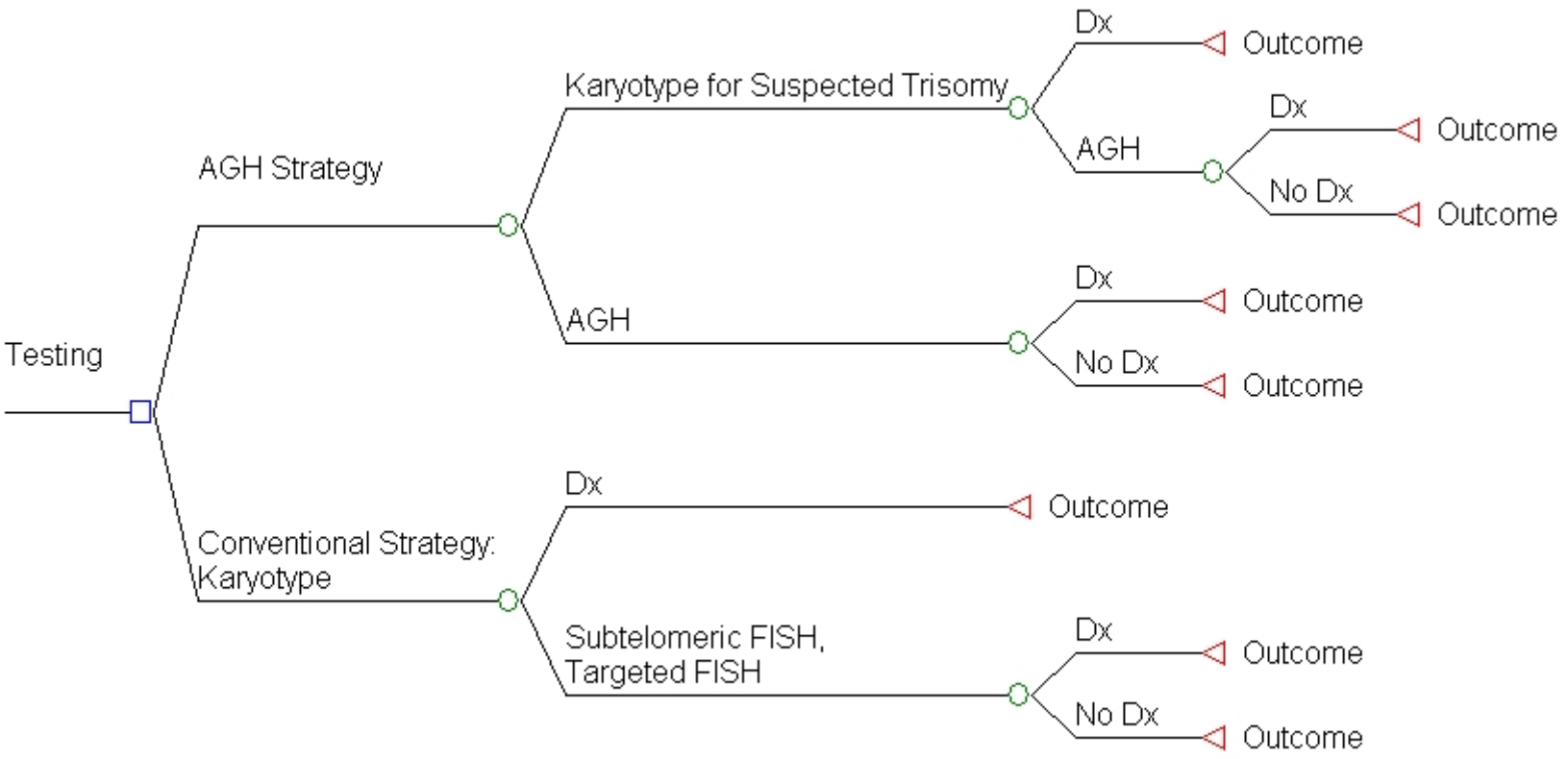
Cost Benefit

Net benefit: incremental WTP - incremental Cost

$$NB_n = \Delta B - \Delta C$$
$$= \frac{\beta_{n\,PDX}}{-\beta_{n\,Cost}} \Delta E - \Delta C$$



Decision analytic model



CBA/CEA Results

Baseline analysis

	Mean AGH Strategy (95% CI)	Mean Conventional Strategy (95% CI)	Mean Difference (95% CI)
Cost	$2,980 (2,727 to 3,254)	$2,763 (2,499 to 3,052)	$217 (172 to 261)
Effectiveness	0.275 (0.245 to 0.228)	0.192 (0.159 to 0.228)	0.082 (0.049 to 0.142)
Incremental cost effectiveness ratio	$2,646 (1,619 to 5,296)		
Benefit in willingness to pay	$1,053 (432-2,828)		
Net benefit	$836 (203 to 1,616)		

Precision Medicine

- Knowledge & effectiveness
  - Knowledge about a patient's genetic profile to prevent, treat or prognosticate disease
- It can be expensive
  - Panel sequencing (409 genes, AmpliSeq) -> ~1,500
  - Whole genome +RNA sequencing -> ~$15,000
- Larger Panels, WGS, etc applied in research, but clinical use limited

Vancouver company offers free gene analysis for cancer patients

CTV National News: Tailoring cancer treatment

A B.C. company is offering Canadian patients a new genetic cancer test at no cost – for now. Avis Favaro reports on personalized medicine.

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CTVNews.ca Staff
Published Sunday, March 13, 2016 8:23PM EDT
Last Updated Monday, March 14, 2016 12:42PM EDT

Starting on Monday, a Vancouver biotechnology company will make an unconventional offer to Canadian cancer patients, by making its new cancer genome test available to 1,500 cancer patients -- at no cost.

The move is part marketing, part testing the potential market in an emerging field of cancer therapy called "personalized medicine."

Contextual Genomics will become the first group in Canada to offer cancer patients a chance at therapy tailored to their genetics.

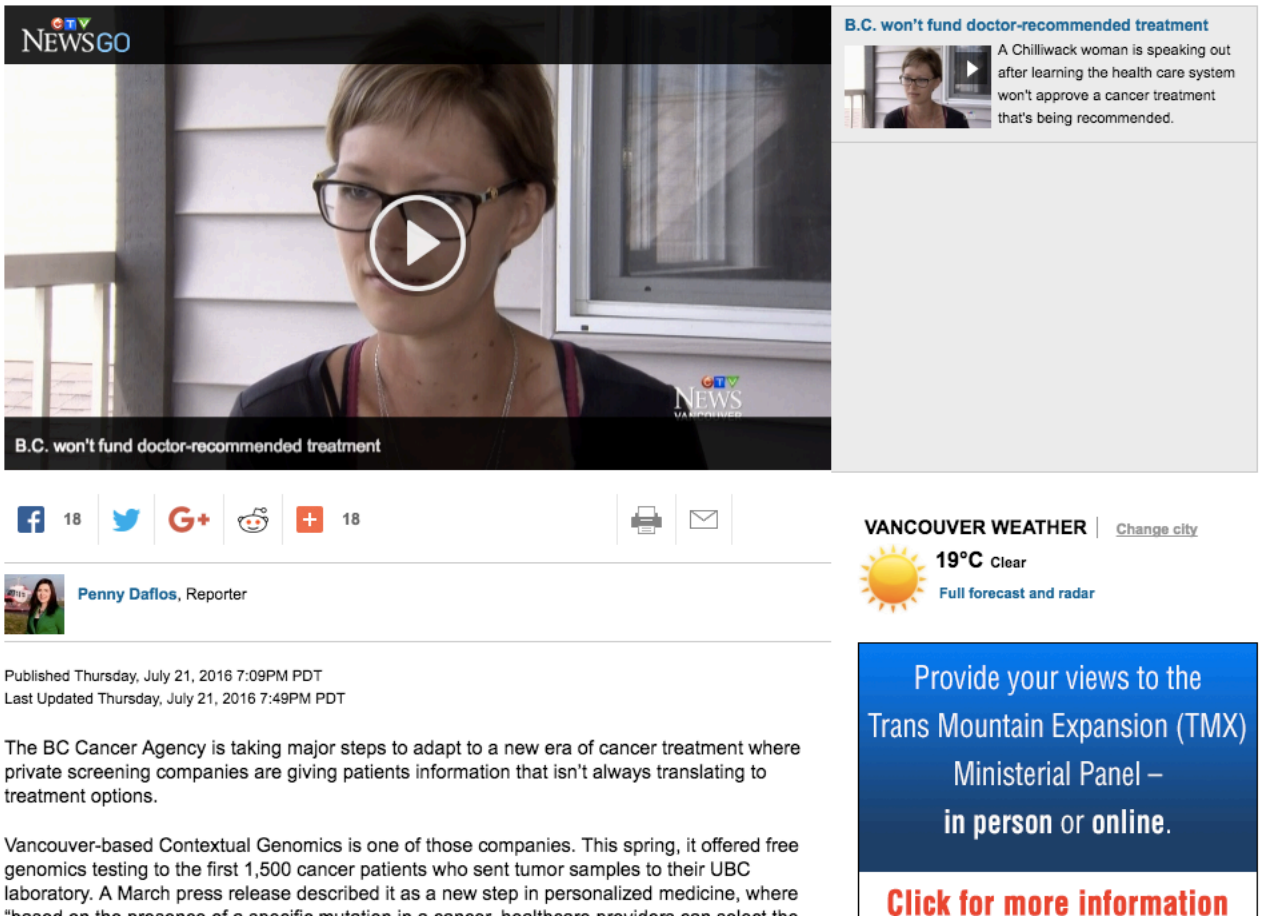
CTV NEWS VIDEO NETWORK

Rhetoric

- "The essence of personalized cancer care can be distilled into the right treatment for the right patient in the right time, and our test will help patients and oncologists determine what is the best option" –CMO, contextual genomics

- "Ten years ago, this would have been science fiction, but today it is actually cost effective to sequence someone's DNA and looking how we can personalize treatment for it" – CMO, contextual genomics

- "A nationally distributed somatic mutation panel can achieve the scale needed to reduce costs, improve quality, and increase availability regardless of where a patient lives" –CEO, PMI Initiative



“The challenge for a publicly funded system is it’s very difficult to justify using very expensive treatment where there is no evidence … of benefit...This comes up not infrequently now that broader genetic tests are becoming available and it’s sometihg we’re actively talking about”

-Dr. Malcolm Moore, President, BC Cancer Agency

Priority setting in Cancer Control

EVIDENCE AND VALUES

Priority Setting

- Process of resource allocation
  - Decision-makers face constrained budgets
- In Canada, it's a devolved responsibility
  - E.g., Prov. cancer agencies
- National organizations (CADTH PCODR)
  - Support priority setting through clinical evidence, cost-effectiveness, and **patient value consequences**

Public engagement

Normative & Pragmatic motivations (Abelson et al, 2003)

1. Normative motivations
   - Legitimacy (acceptance)
   - Transparency (evidence used)
   - Accountability (reason-giving/mechanism for appeal)

2. Pragmatic motivations
   - Popular support for policies

Up to here

1. Priority setting provides the rationale of using public/patient engagement.
2. It allows for ‘something more’
   - Consistent with a extra-welfarist framework
3. Individuals can attach important value to information from genetic testing

Question:

Should value of genomic information have a role in priority setting?

UTILITY FOR KNOWLEDGE

...a contested criterion

Personal utility

- The utility of individuals and/or families for genomic information (Grosse et al, 2010)

- Reasons for consideration (Bunnick et al, 2015)
  - Used as a moral justification for direct access to commercial genomic testing
  - Right to knowledge of individual genomic results in research

Proposed ethics perspective

"In the absence of clinical validity and reasonable potential use of information, there is no personal utility"

Journal of Medical Ethics, Bunnick et al, 2015.

- Can be reasonably used for decisions, actions, or self-understanding
- Affected individuals are not always in best position to judge
- "....*experts should determine whether a particular genomic test can provide the clinical or personal utility sought*"

...on the other hand

- Information improving patient understanding or widening of therapeutic choice (Buchanan et al, 2013)
  - Enhances sense of control, informs self-identity (Rogowski et al, 2010; Foster et al, 2009)
  - Reassurance or anxiety relief (Asch et al, 1996; Caughey, 2005)
  - Reducing diagnostic odyssey (Wordsworth et al, 2007; Regier et al, 2009)
  - Benefit of process related attributes (Ryan et al, 2007)

The genomic technology

- Next generation genomic sequencing
  - Predictive therapy, prognostic therapy, hereditary cause of disease

- Potential of incidental findings
  - Information on diseases not related to current diagnosis
    - E.g., Test for Lynch syndrome, find risk for Long QT syndrome (treatable) and Alzheimer's (effective treatment not available).

Preference-based utility for knowledge

	Option A	Option B	No information
Disease Risk *More disease will be identified if the lifetime risk is lower*	Diseases with a **80% lifetime risk or higher**	Diseases with a **5% lifetime risk or higher**	No information
Disease Treatability	Recommended effective medical treatment and lifestyle change	Recommended effective medical treatment only	No information
Disease Severity *Health consequences of the diseases you may develop*	Mild health consequences	Moderate health consequences	No information
Carrier Status *Disease risk not affecting you but can affect your family*	Does not provide information on carrier status	Information on if your family members could be affected	No information
Cost to you	$425	$1500	$ 0
	Option A ☐	**Option B ☐**	**No Information ☐**

Aim: What is the predicted uptake and WTP of different strategies for returning incidental findings? Regier et al, 2015

	New Policy	Prevailing Policy	Incremental willingness to pay (95% CI)	Uptake of New Policy Alternative(s) (95% CI)
Scenario 1	Return results only for disorders with: Recommended effective medical treatment Severe health consequences high penetrance mutations	Information on incidental findings is not returned	$445* (322,567)	66%* (63,71)
Scenario 2	Return results only for disorders with: Recommended effective medical treatment and lifestyle change Severe health consequences high penetrance mutations	Information on incidental findings is not returned	$641* (520,762)	73%* (69,77)
Scenario 3	Return results only for disorders with: Any treatability level Severe health consequences high penetrance mutations Or only disorders with: Recommended effective medical treatment Severe health consequences high penetrance mutations Based on patient preference	Recommended effective medical treatment only; Severe health consequences; 80% lifetime risk or higher	$280* (248, 313)	Medical & non medical treatment 27%* (24,29) *Medical treatment only* 49%* (45,52) *Total uptake* 76%* (72,79)

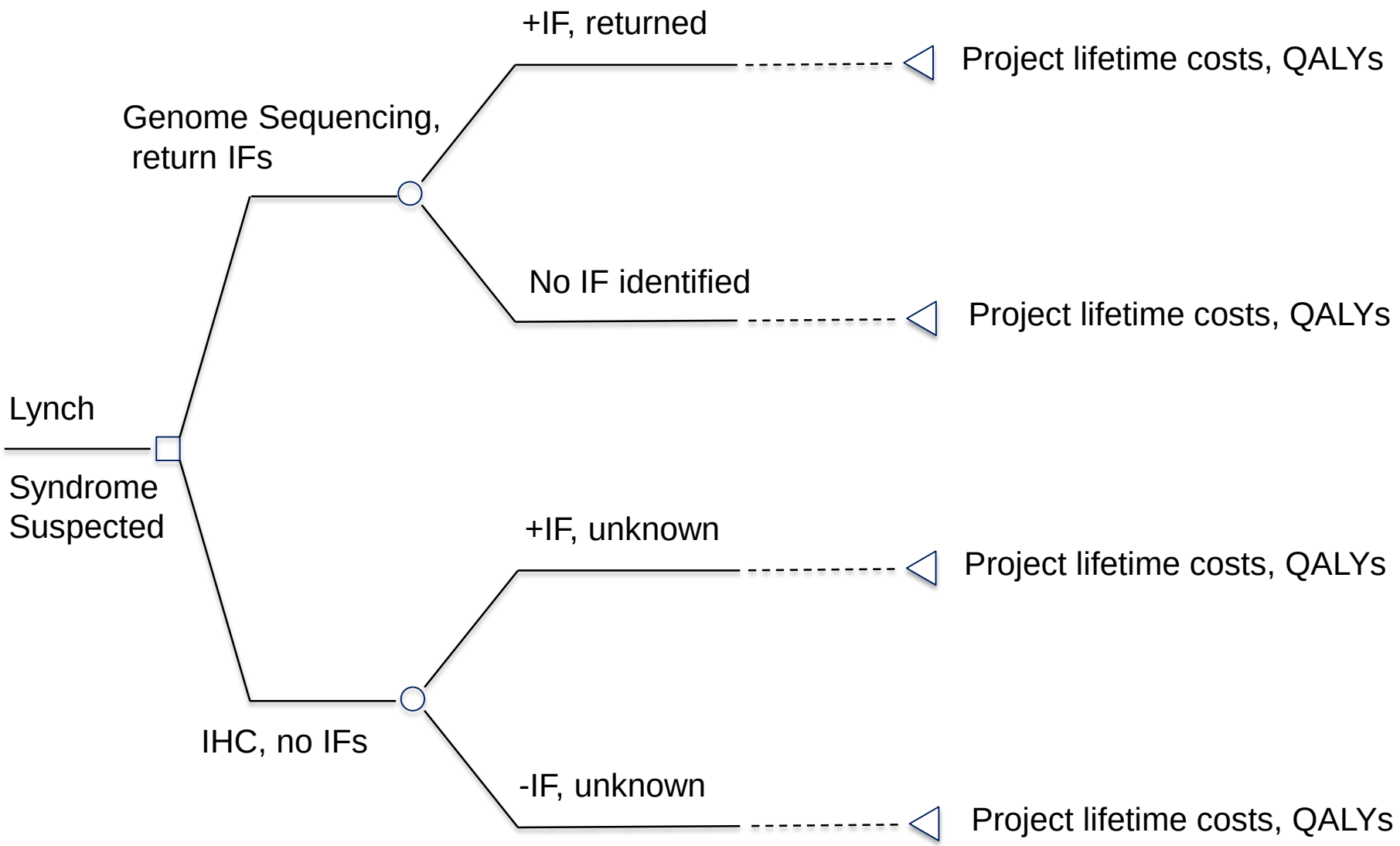
*P-value of <0.03, 95% CI = 95% Confidence interval. Willingness to pay is derived from the estimates of the mixed logit statistical model using the compensating variation formula. All estimates are in 2013 Canadian dollars. Estimates are in 2013 Canadian dollars.

Cost-effectiveness

- What is the ΔC/ΔQALY of returning secondary findings vs. usual care in the context of NGS versus IHC for Lynch Syndrome screening ?

AND

- What is the net monetary benefit when allowance is made for personal utility? Where:
  - QALYs represent utility of health gain
  - λ is decision-maker's WTP for a health gain
  - WTP provide a quantity for value of knowledge



IHC genes: MLH1,2,6; PMS2
Genome: add autosomal dominant CRCP mutations

CEA/NB Results

Parameter	Mean	95% Credible Interval
Baseline		
ΔCost of NGS CRCP screening	$5,676	3,441to 9,931
ΔCost of NGS CRCP screening + IFs	$11,417	9,061to 15,683
ΔQALY of NGS CRCP screening	0.128	0.036 to 0.295
ΔQALY of IFs	0.0014	
ΔQALY NGS CRCP+IFs	0.1293	0.036 to 0.295
ICER NGS CRCP screening	$44,343 per QALY	
ICER NGS CRCP screening+IFs	$88,298 per QALY	38,135 to 367,807
NMB CRCP+IFs λ=100,000 per QALY	$1,521	-8,894 to 17,185
NMB of CRCP+IFs λ=$100,000 per QALY ξ=$641 for incidental findings	$2,162	-8,619 to 18,268

Cost of diagnostic whole genome sequencing = $5,840; NMB=net monetary benefit; IF=Incidental Findings

Discussion

- CUA as a reference case is here to stay
- Priority setting and extra-welfarism
  - Provide opportunity to consider something more
- Individuals value knowledge apart from improved health
- Should WTP for information (+QALYs) be used in priority setting as a form of public input?
- Is there an argument to allow patients to personally pay for this information?

Thank-you

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Phenotype	Number detected	Incremental $	Incremental QALYs	Net Monetary Benefit
Colorectal Cancer Polyposis Syndromes	1540	$5,676	0.128	$7,654
Familial hypercholesterolemia	29	$7,392	0.53	$46,160
Hypertrophic and dilated cardiomyopathy	10	$39,881	1.10	$70,782
Arrhythmogenic right ventricular cardiomyopathy	9	$107,493	0.31	-$75,379
Malignant hyperthermia susceptibility	4	$5,133	0.01	-$3,186
Long QT Syndromes	2	$59,046	0.18	-$40,220
Other, rare conditions (combined)	5	$75,863	0.00	-$75,222
Total (IFs excluding CRCP)	***58***	***$5659***	***0.0014***	***-$4,962***
Total (all conditions)	***1598***	***$11,417***	***0.129***	***$2,162***