Exploring the Link between Genomic Testing Decisions and Quality of Life When Diagnosing Rare Childhood Disorders: A Sequential Stated Choice Experiment

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Background

Rare diseases are defined by their prevalence, each affecting fewer than 5 to 7 in 10,000 people.[1] While individually rare, cumulatively, 1 in 16 people suffer from a rare disease worldwide.

Rare diseases predominantly manifest in children and most are caused by genetic factors, although etiologic diagnoses are difficult and costly to establish. Patients and families face a diagnostic odyssey when searching for a genetic etiology.[2]

Parents value etiologic diagnoses, even in the absence of treatment change.[3] No stated choice studies have measured if these values depend on health state.

Research question

What are parents' preferences for genomic testing to diagnose rare diseases conditional on children's health-related quality of life?

Methods

Sequential mixed methods study

Step 1: Qualitative focus groups[3] with 33 parents in Vancouver, Canada and Oxford, England (n_{CAN}=3, n_{UK}=1)

"… … if my child was in an extreme amount of pain, or I could see that there was severe impact on their life, then I would go to… almost whatever lengths to get an answer."" [FG1P6]

"For me it comes down to the severity of the issue my kid is facing…. If my kid was significantly disadvantaged, having problems or particularly in pain, and I really believe that this was going to give me benefit and help me manage the situation, I don't care what it costs, quite honestly…" (FG2P2)

Step 2: Sequential 2-part stated choice experiment, based on focus group findings and refined via think-aloud interviews (n=10).

Survey design and administration: Bayesian D-efficient experimental design (32 tasks divided across 4 blocks) with priors based on pilot study (n_{CAN}=100, n_{UK}=111). Final survey administered to CAN and UK publics from Sept 2022 to Jan 2023 using quota sampling via a market research firm.

Part 1: Choice of preferred health state

Attributes: Health Utilities Index Mark 2 (HUI2)[4] + duration

For your child, which quality of life profile do you prefer?

Health State A	Health State B
7 years with health problems before new genetic testing	3 years with health problems before new genetic testing
Requires equipment to see or hear or speak	Blind, deaf, or mute
Walks, bends, lifts, jumps, or runs with some limitations but does not require help.	Requires the help of another person to walk or get around and requires mechanical equipment as well.
Eats, bathes, dresses, or uses the toilet independently with difficulty	Eats, bathes, dresses, or uses the toilet independently with difficulty
Generally happy and free from worry	Almost always fretful, angry, irritable, anxious, depressed
Learns and remembers very slowly and usually requires special educational assistance	Learns and remembers school work normally for age
Occasional pain, discomfort can be relieved without disruption of usual activities	Occasional pain, discomfort can be relieved without disruption of usual activities
○	◉

Choice Question 1 (first page)

Part 2: Choice of preferred genomic test

Attributes: Likelihood of diagnosis; turnaround time; concordance between laboratory and doctor's interpretations of test results; and cost

Imagine your child is in the Health State you just selected (A or B).

A new genetic test may be able to diagnose whether your child's disease is genetic. Which testing option do you prefer for your child?			
	Option 1	Option 2	Neither Option
Likelihood of receiving a genetic diagnosis with the new genetic test	20 out of every 100 children	40 out of every 100 children	
Time spent waiting for test results	3 months	3 months	
Laboratory and doctor interpretation that your child's genetic variant caused their disease	Laboratory: very high likelihood Doctor: very high likelihood	Laboratory: moderate likelihood Doctor: very high likelihood	
Out of pocket cost to you	$1,000	$1,000	$0
	○	◉	○

Choice Question 2 (next page)

Modelling choice data

Applies a previously developed framework[5] for estimating a two-stage decision process that designs both sequential stages as independent tasks and incorporates the probability of choice from the first stage (A) into the second stage (B) choice. Parameter estimation is via FIML.

Utility functions:

$$U_{ni}^{t} = V_{ni}^{t} + \varepsilon_{ni}^{t}$$

t: part 1 or 2
n: respondent
i: option

Assumes errors are IID extreme value type I

Part 1 – MNL (duration interacted with attribute levels for anchoring)

$$V_{part\ 1,ni} + \varepsilon_{part\ 1,ni} = \alpha_{years\ in\ health\ state} \cdot years\ in\ health\ state + years\ in\ health\ state \cdot [ASC_{left-to-right\ bias,part\ 1} + \Sigma_{L-1=2}\beta_{senses} \cdot senses + \Sigma_{L-1=4}\beta_{mobility} \cdot mobility + \Sigma_{L-1=3}\beta_{self\ care} \cdot self\ care + \Sigma_{L-1=4}\beta_{emotional\ state} \cdot emotional\ state + \Sigma_{L-1=3}\beta_{learning} \cdot learning + \Sigma_{L-1=4}\beta_{pain\ and\ discomfort} \cdot pain\ and\ discomfort] + \varepsilon_{part\ 1,ni}$$

The predicted probability of the chosen option in part one:

$$P_{part\ 1,ni} = \frac{exp(\mu V_{part\ 1,ni})}{\sum_{j=1}^{n} exp(\mu V_{part\ 1,nj})}$$

enters the utility function of part two:

Part 2 – nested logit (nests consider any test versus no test)

$$V_{part\ 2,ni} + \varepsilon_{part\ 2,ni} = ASC_{left-to-right\ bias,part\ 2} + ASC_{any\ test} + \Sigma_{L-1=2}\beta_{waiting\ time} \cdot waiting\ time + \Sigma_{L-1=2}\beta_{likelihood\ of\ diagnosis} \cdot likelihood\ of\ diagnosis + \Sigma_{L-1=2}\beta_{interpretation} \cdot interpretation + \beta_{cost} \cdot income\ multiplier \cdot cost + \widehat{P_{part\ 1,ni}} \cdot [ASC_{any\ test} + \Sigma_{L-1=2}\gamma_{P\cdot waiting\ time} \cdot waiting\ time + \Sigma_{L-1=2}\gamma_{P\cdot likelihood\ of\ diagnosis} \cdot likelihood\ of\ diagnosis + \Sigma_{L-1=2}\gamma_{P\cdot interpretation} \cdot interpretation + \gamma_{P\cdot cost} \cdot income\ multiplier \cdot cost] + \varepsilon_{part\ 2,ni}$$

Where $income\ multiplier = (\frac{income}{\widehat{income}})^{\lambda_{income}}$

Results

Study characteristics

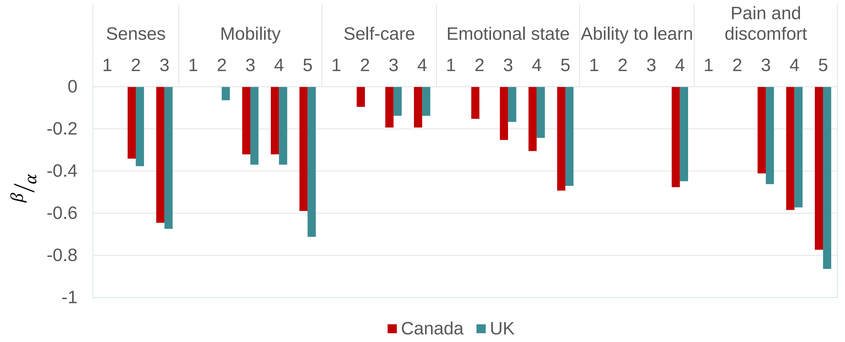
Overall response rate
CAD: 32%
UK: 37%

Completion rate
CAD: 44%
UK: 51%

Characteristic	n (%)	Canada 3,231	United Kingdom 3,048
Male		1557 (48%)	1464 (48%)
Female		1646 (51%)	1564 (51%)
Non-binary		28 (1%)	20 (1%)
Age >65		783 (24%)	628 (21%)
Income <$30K or <£14K		569 (18%)	382 (13%)
Parent or guardian		1970 (61%)	2018 (66%)
Genetic testing history		406 (13%)	362 (12%)

Part 1: Health state utility values throughout diagnostic odyssey

In both jurisdictions, respondents most valued children's senses, mobility, and avoidance of pain and discomfort, above other quality of life domains.



All attribute levels significant at p-value<0.05. Dimensions based on modified HUI2. Estimates based on consistent gradient models.

Part 2: Values for genomic testing attributes

Independent of choice of health state, respondents preferred any genomic test, shorter waiting times, lower costs, and less discordance in the interpretation of test results.

Effect of choice of health state on values for genomic testing

Genomic testing decisions are influenced by children's underlying quality of life.

Dimension	Level	CAN (n=3,231) Coeff.	CAN (n=3,231) SE	UK (n=3,048) Coeff.	UK (n=3,048) SE
$\widehat{P_{part\ 1,ni}}$ * Any test	Any test	1.038***	0.159	0.970***	0.157
	Neither test	Ref.	-	Ref.	-
$\widehat{P_{part\ 1,ni}}$ * Wait time	3 month	Ref.	-	Ref.	-
	8 months	-0.025	0.144	-0.560***	0.141
	18 months	-0.310***	0.107	-0.624***	0.105
$\widehat{P_{part\ 1,ni}}$ * Likelihood of diagnosis	10%	Ref.	-	Ref.	-
	20%	0.022	0.116	0.246**	0.110
	40%	0.179	0.112	0.699***	0.113
$\widehat{P_{part\ 1,ni}}$ * Doctor and laboratory interpretation	High and high	Ref.	-	Ref.	-
	High and moderate	0.021	0.116	-0.122	0.092
	High and unknown	0.179	0.112	-0.193*	0.117
$\widehat{P_{part\ 1,ni}}$ * Cost		0.767***	0.298	0.677**	0.315

*p-value<*0.10, **0.05, ***0.01*

Coefficients reveal increased sensitivity to changes in attribute levels conditional on perception of better relative health in Part 1.

Conclusions

Parents' decisions to have their children undergo genomic testing depend not only on test attributes and results, but on quality of life.

These underlying values will drive genomic testing uptake in clinical settings.

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1. Auvin S, Irwin J, Abi-Aad P, Battersby A. The Problem of Rarity: Estimation of Prevalence in Rare Disease. Value Health. 2018 May;21(5):501-507; 2. Bauskis A, Strange C, Molster C, Fisher C. The diagnostic odyssey: insights from parents of children living with an undiagnosed condition. Orphanet J Rare Dis. 2022 Jun 18;17(1):233; 3. Pollard S, Weymann D, Dunne J, Mayanloo F, Buckell J, Buchanan J, Wordsworth S, Friedman JM, Stockler-Ipsiroglu S, Dragojlovic N, Elliott AM, Harrison M, Lynd LD, Regier DA. Toward the diagnosis of rare childhood genetic diseases: what do parents value most? Eur J Hum Genet. 2021 Oct;29(10):1491-1501; 4. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI): concepts, measurement properties and applications. Health Qual Life Outcomes. 2003 Oct 16;1:54; 5. Huynh E, Swait J, Lancsar E,Modelling online job search and choices of dentists in the Australian job market: Staged sequential DCEs and FIML econometric methods,Journal of Choice Modelling, Volume 44, 2022, 100372.