BC CANCER
Provincial Health Services Authority

THE UNIVERSITY OF BRITISH COLUMBIA
Academy of Translational Medicine
Faculty of Medicine

Real-world economic evaluation of genome-wide sequencing for developmental and seizure disorders: Evidence from Canada

Dean A. Regier, Rosalie Loewen, Brandon Chan, Morgan Ehman, Samantha Pollard, Jan M. Friedman, Sylvia Stockler-Ipsiroglu, Simone Race, Clara van Karnebeek, Alison M. Elliott, Nick Dragojlovic, Larry D Lynd, **Deirdre Weymann**

BC Cancer Research Institute, Vancouver, Canada

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Public Health: Health Services Research Seminar - Real-world economic evaluation of genome-wide sequencing for developmental and seizure disorders: Evidence from Canada

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NAME	COMPANY	RELATIONSHIP
Deirdre Weymann, MA	Illumina	Speaking

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William Daehler, MA
Jeffrey Hoch, PhD

Acknowledgments and disclosures

I am from Vancouver, British Columbia and have the privilege to reside and work on the traditional, ancestral and unceded territories the Coast Salish peoples, including Sḵwx̱wú7mesh Úxwumixw (Squamish), Səl̓ilw̓ətaʔɬ (Tsleil-Waututh), Xʷməθkʷəy̓əm (Musqueam), and Stó:lō Nations

I co-direct IMPRINT Research Consulting Ltd., and have received consulting funds from Astra Zeneca Canada and Birota Economics Group, and travel funding from Illumina.

This study was funded by Genome British Columbia (GEN001) and the Canadian Network for Learning Healthcare Systems and Cost-effective ‘Omics Innovation: CLEO is supported by Genome British Columbia / Genome Canada [G05CHS] and our co-funding partners: Genome Quebec, Terry Fox Research Institute, BC Cancer’s Personalized OncoGenomics Program (POG), Institute of Health Economics, Simon Fraser University, Ontario Institute for Cancer Research, Canadian Centre for Applied Research in Cancer Control (ARCC), National Cancer Institute, Krembil Foundation, Australian Research Council, and Roche.

Learning objectives

1. Understand challenges driving uncertainty in the value of genomic testing for diagnosing rare diseases in children

2. Describe the real-world diagnostic outcomes and cost trajectories of standard of care testing for children with developmental and seizure disorders

3. Understand the potential cost-effectiveness of earlier tier genomic testing and remaining evidence gaps

Article

Real-world diagnostic outcomes and cost-effectiveness of genome-wide sequencing for developmental and seizure disorders: Evidence from Canada

Dean A. Regier [1 2], Rosalie Loewen [2], Brandon Chan [2], Morgan Ehman [2], Samantha Pollard [2], Jan M. Friedman [3 4], Sylvia Stockler-Ipsiroglu [4 5 6], Clara van Karnebeek [5 7], Simone Race [6], Alison M. Elliott [3 4], Nick Dragojlovic [8], Larry D. Lynd [8 9], Deirdre Weymann [2]

Translational medicine in Canada

New Drug Submission:

- Preclinical and clinical studies on safety and efficacy
- Manufacturing, packaging, and labelling details
- Label information (therapeutic claims and side effects)

Health Canada HPFB Review

Risk-benefit evaluation of drug by reviewing data on:

- Safety
- Effectiveness
- Quality

*Successful review leads to NOC

*Accelerated review and approval via NOC/c

PMPRB Review

Monitors drug prices for duration of patent

Process:

- PMPRB Filing
- Scientific Review
- Price Review
- Investigation

CDA-AMC *(formerly CADTH)* **and pCODR, INESSS**

Reimbursement recommendations

Deliberative framework:

- Clinical benefit
- Patient values
- Cost-effectiveness
- Feasibility of adoption

Reimbursement Decision

- Jurisdiction-based

Background

Rare diseases affect 1 in 16 people

Etiologic diagnoses are difficult and costly to establish

Parents value etiologic diagnoses, even in the absence of treatment change[1]

"… I think you'd just get to the point where you'd forgo any other concerns, just like, "What is it? I need to know."" [FG1P2]

"just that peace of mind saying I know what the problem is…" (FG4P11)

Genome-wide sequencing (GWS) technologies improve diagnostic yield, but downstream impacts are uncertain

1. 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.

What drives uncertainty?

Small benefitting populations

Short term outcomes data

Non-traditional trial designs

Rapidly changing technology costs

Data limitations

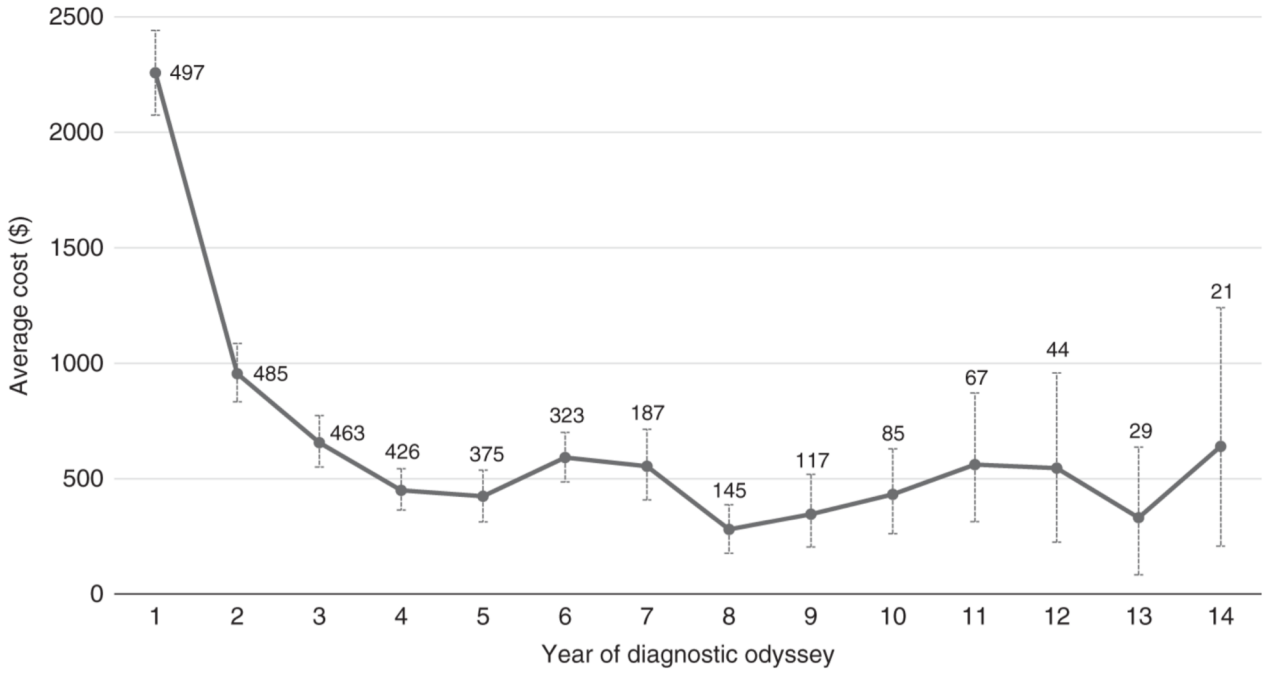
Uncertain value of a diagnosis

Clinical pathways in BC

In BC, the diagnostic odyssey costs upwards of C$5,596[2] per patient

The province publicly reimbursed last-tier ES in 2016 while evidence continued to emerge from research studies

On average, patients wait 3 years to access clinical ES



Annual average per-patient non-GWS diagnostic testing costs for TIDE cohort (*n*=498). Error bars represent 95% confidence intervals. Means and 95% confidence intervals were estimated using bootstrapping. Figures above the error bars indicate the number of observations used to calculate the mean cost at each time point. *GWS* genome-wide sequencing.

2. N Dragojlovic, et al. The cost trajectory of the diagnostic care pathway for children with suspected genetic disorders. 2020. Genet Med.

Research question

What is the real-world cost-effectiveness of streamlining access to genome-wide sequencing compared to current clinical practice?

Focus on: developmental and seizure disorders

Real-world evidence

"Clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world data" – *U.S. FDA*

RWD is…

"Data relating to patient health status and/or the delivery of health care routinely collected from *a variety of sources.*"

3. U.S. Food & Drug Administration. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence
4. Swift B, Jain L, White C, Chandrasekaran V, Bhandari A, Hughes DA, Jadhav PR. Innovation at the Intersection of Clinical Trials and Real-World Data Science to Advance Patient Care. Clin Transl Sci. 2018 Sep;11(5):450-460.

Real-world data sources

COHORT IDENTIFICATION

1

Last tier clinical ES recipients

manually abstracted

C&W Biochemical Diseases department records (n=118)

Paper records and electronic tracking data for all patients who received publicly reimbursed ES, including patient characteristics, reason for referral, blood draw and report dates, number of samples, test results and changes in clinical management

2

Non-ES/GS standard care recipients

de-identified and previously abstracted

C&W TIDE-BC database (n=393)

Clinical research database capturing patient and clinical characteristics, healthcare resource utilization (including service dates and types), costs, and diagnostic outcomes for all consented patients, excluding ES/GS recipients

OUTCOMES ESTIMATION

3

Real-world provincial resource utilization

manually abstracted

BC CareConnect database

Province-wide electronic medical records capturing information on all diagnostic services rendered in BC (incl. diagnostic imaging, physiologic tests, specimen collection, genetic testing and laboratory testing) and corresponding results

4

Detailed clinical and institutional information

manually abstracted

C&W Cerner PowerChart database

Institutional electronic medical records and documents capturing detailed clinical information on patient phenotypes and healthcare resource utilization for diagnostic services rendered at C&W

5

Pricing and unit cost data

manually and previously abstracted

BC Ministry of Health
Medical & laboratory services fee schedules

C&W Biochemical Diseases
Costs captured by internal lab requisition tracking

Literature sources & list prices

Analytic approach

Decision analytic model to evaluate cost-effectiveness

RWD informs model structure and parameterization

- Cost parameters based on generalized estimating equation (GEE) models
- Transition probabilities informed by diagnostic yield estimation
- Time to events estimated with Kaplan-Meier analysis and Weibull regression

Probabilistic analysis via Monte Carlo simulation and sensitivity analysis (key parameters, horizon, bioinformatics)

What is cost-effectiveness analysis?

Systematic and comparative analysis of the cost and effectiveness of at least two courses of action

Incremental costs: $\Delta C = C_{new} - C_{old}$ — What are the costs of A compared to B?

Incremental effects: $\Delta E = E_{new} - E_{old}$ — What are the consequences of A compared to B?

What is cost-effectiveness analysis?

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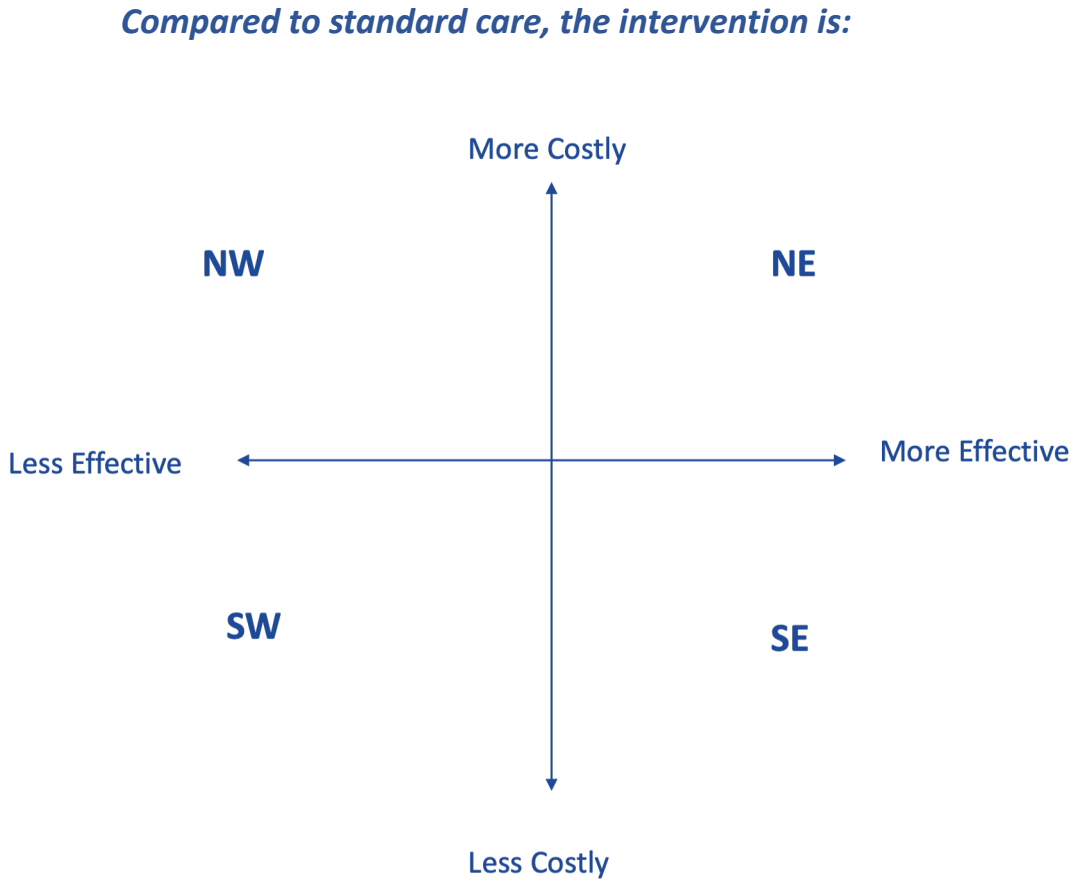


What is cost-effectiveness analysis?

Systematic and comparative analysis of the cost and effectiveness of at least two courses of action

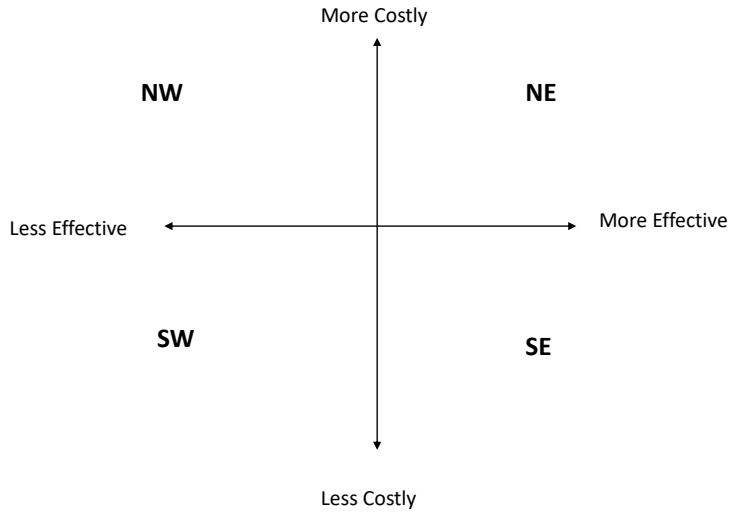
Incremental costs: $\Delta C = C_{new} - C_{old}$

Incremental effects: $\Delta E = E_{new} - E_{old}$

$$ICER = \frac{\Delta C}{\Delta E}$$ Additional cost for each unit of effectiveness gained, use a threshold to determine value-for-money

Or $NMB = \Delta E * \lambda - \Delta C$ Positive or negative?

Compared to standard care, the intervention is:



Model structure

Viewpoint: public healthcare payer

Alternatives:

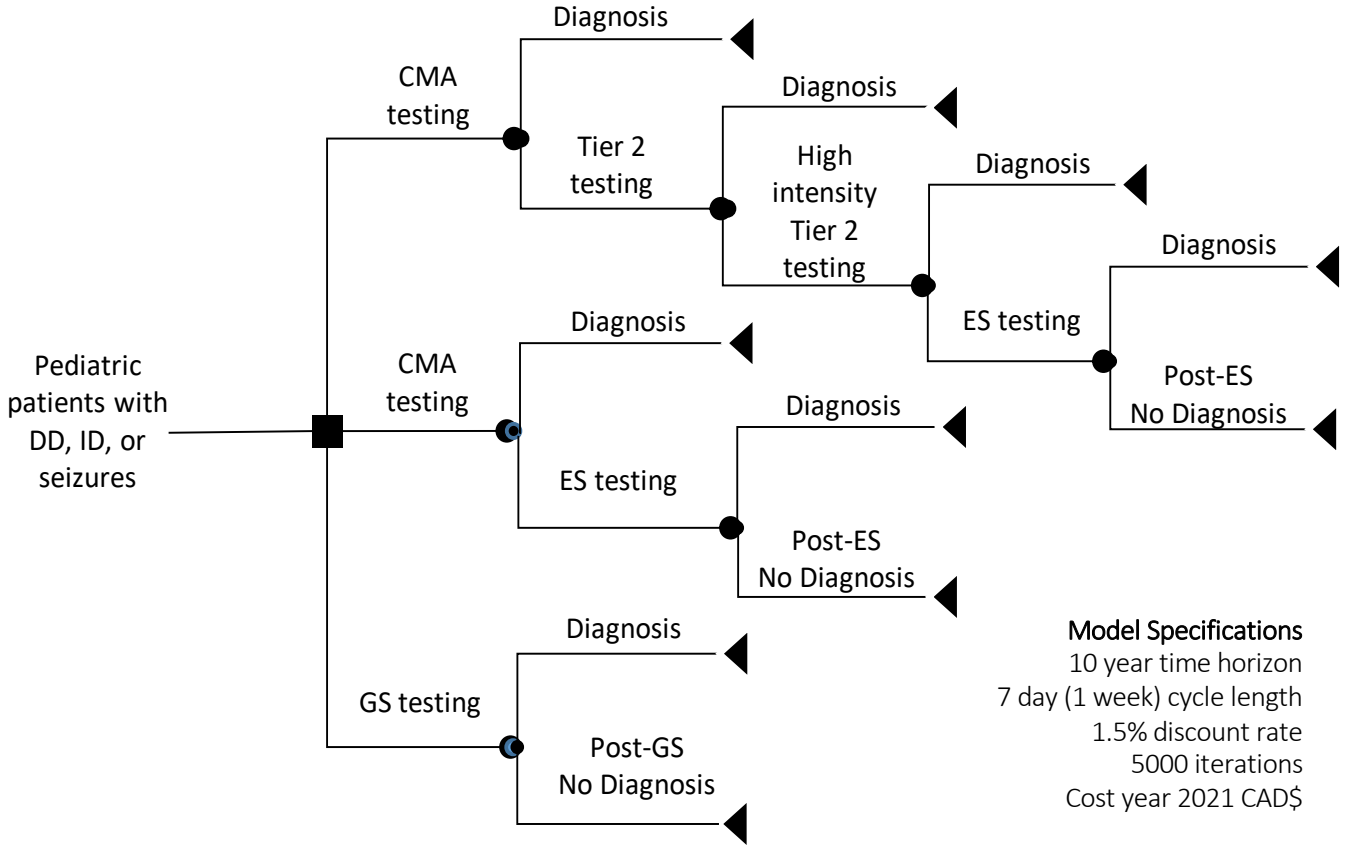
Current standard of care (SOC)

CMA followed by second tier testing, including single gene testing, biochemical tests, panel testing, and last-tier ES access

Streamlined exome sequencing (ES)

CMA followed by ES, with single gene testing and panels eliminated in favor of streamlined access to ES

First-tier genome sequencing (GS)



Real-world parameters

Probabilities of diagnosis			
Diagnosis from CMA	12%	Beta	TIDE-BC cohort
Diagnosis from SoC Tier 2 testing	8%	Weibull	TIDE-BC cohort
Diagnosis from SoC final tier ES	40%	Beta	C&W clinical ES cohort
Diagnosis from Tier 2 ES	45%	Beta	Assumed (based on SoC)
Diagnosis from Tier 1 GS	51%	Beta	Assumed (based on SoC)
Wait times			
Wait time post-CMA	7 weeks (SD: 9)	Gamma	C&W clinical ES cohort
Wait time post-ES	20 weeks (SD: 16)	Gamma	C&W clinical ES cohort
Wait time post-GS	20 weeks (SD: 16)	Gamma	Assumed (same as SoC final tier ES)
SoC Tier 2 testing time	Time-varying	Weibull	TIDE-BC cohort
SoC ramp-up of Tier 2 testing pre ES	19 weeks	-	C&W clinical ES cohort
Costs			
Price of CMA	$868	-	Internal estimate and published literature[5]
Price of ES	$4,065 (SD: $1,236)	Gamma	C&W clinical ES cohort
Price of GS	$6,085 (SD: $2,558)	Gamma	Internal estimate
Weekly costs (pre/post testing and pre/post diagnosis)	Time-varying	Gamma	Predicted from GEE model

5. Regier DA, Friedman JM, Marra CA. The American Journal of Human Genetics. 2010;86(5):765-772.

Results: Cohort characteristics

		TIDE-BC		BC Publicly Reimbursed ES		P-value
Subjects (n=501)	*n (%)*	411	82	90	18	-
Sex, female	*n (%)*	153	37	40	4944	0.200
Age at earliest diagnostic service	*μ (σ)*	2.55	3.38	2.88	3.10	0.430
Number of concomitant disorders	*μ (σ)*	4.69	2.74	4.14	1.53	0.066
Phenotype	*n (%)*					0.273
Developmental disorder		275	67	59	66	
Seizure disorder		62	15	21	23	
Both		37	9	10	11	
Missing		37	9	0	0	
Trio-based GWS*	*n (%)*	-	-	16	18	-

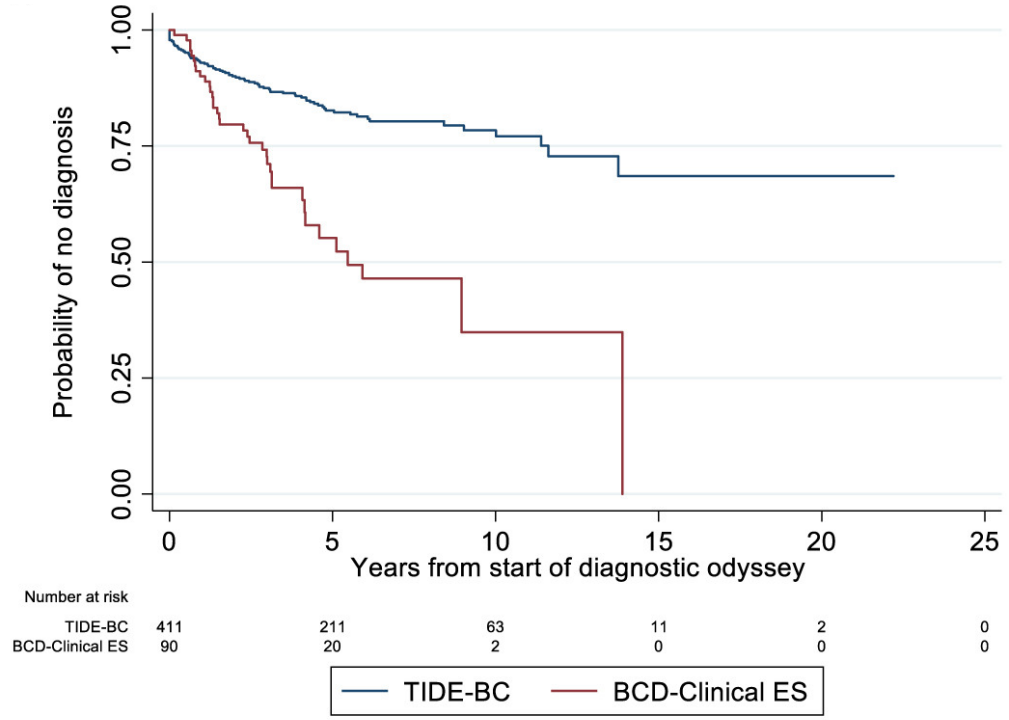
Significance level: p<0.05
p-value from Chi square tests for categorical variables and Mann-Whitney-U tests for continuous variables
**number of samples sequenced was missing for 63% of patients*

ES recipients were more likely to:

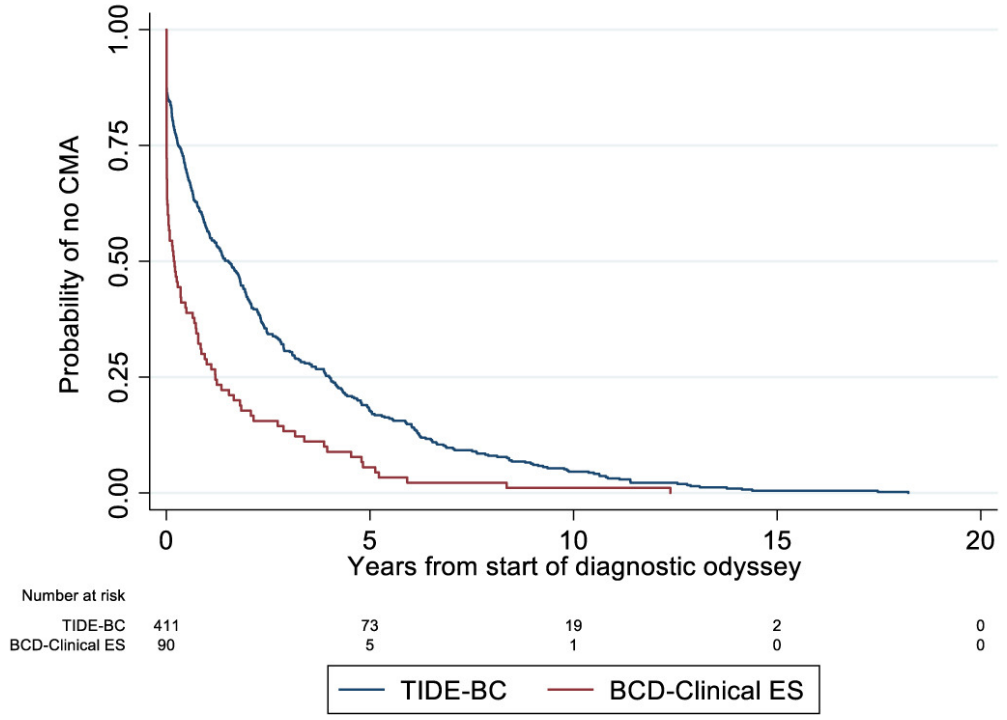
Have more concomitant disorders

Results: Diagnostic outcomes

Time from earliest diagnostic service to diagnosis

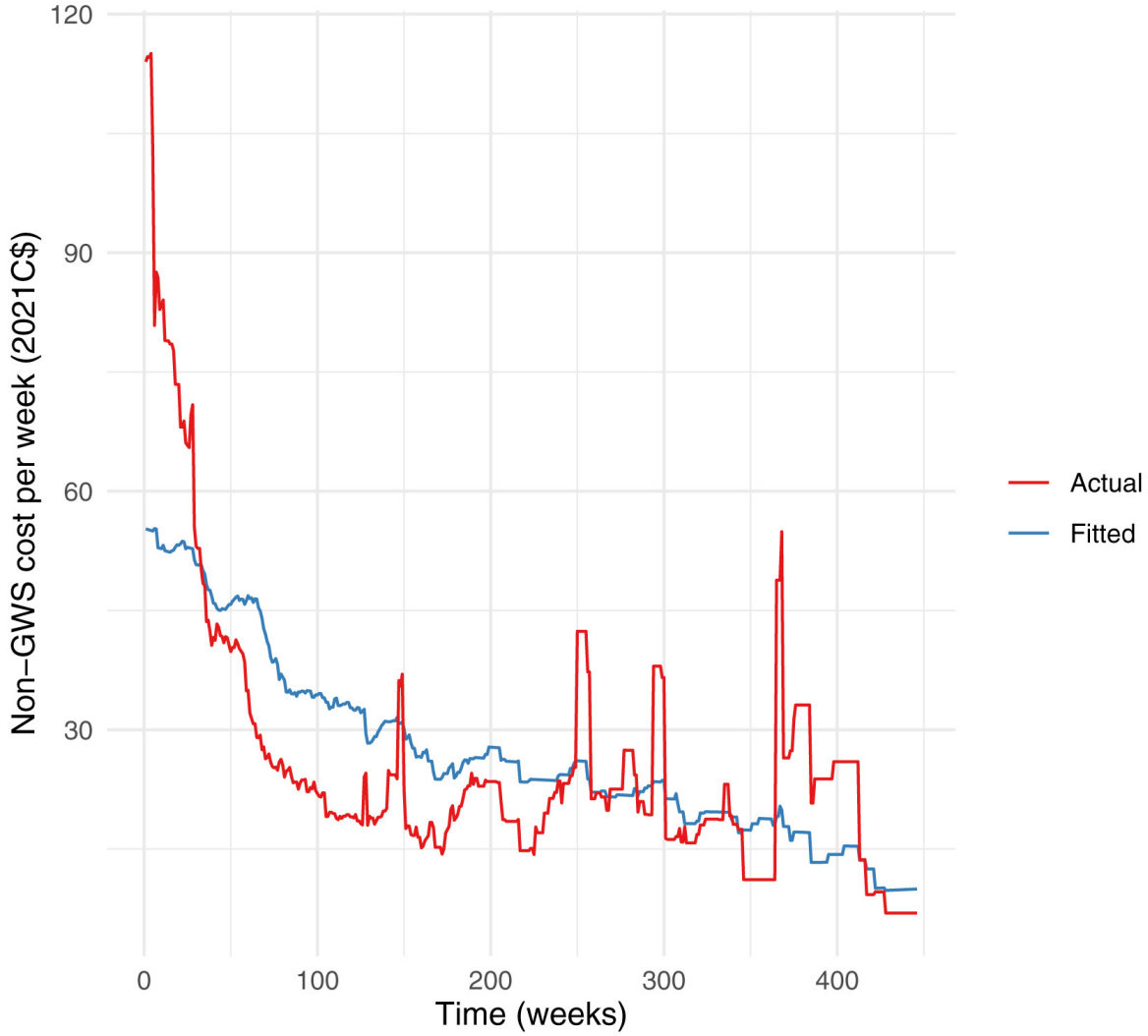


Time from earliest diagnostic service to CMA



		TIDE-BC		Publicly Reimbursed ES		P-value
Time to diagnosis (years)	*μ (σ)*	17.05	0.64	7.41	0.84	<0.001
Diagnostic yield	*n (%)*	77	19	36	40	<0.001

Results: Cost trajectory



Mean total per-patient costs for last-tier ES recipients were C$12,026 (95% CI: 10,171, 12,880)

Mean cost of ES was C$4,065 (95% CI: 3,842, 4,288)

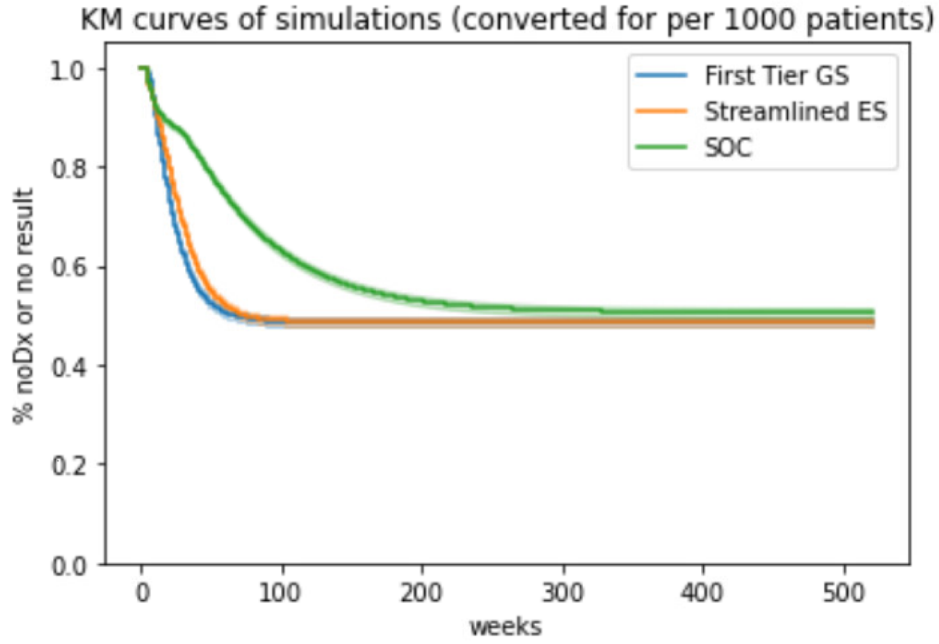
GEE models estimated that:

- Most costs occurred at beginning of diagnostic odyssey
- ES significantly impacted patient cost trajectories

Results: Projected costs & diagnostic yield

	Mean cost (SE)	Mean yield (SE)	Mean time to diagnosis (SE)
SOC	$11,683 (1,267)	49.4 (4.5)	72 weeks (62.7)
Streamlined ES	$8,913 (1,302)	51.3 (4,4)	28 weeks (18.6)
First-tier GS	$10,456 (2,716)	51.3 (4.9)	24 weeks (16.0)

SE: standard error; ES: exome sequencing; SOC: standard of care; GS: genome sequencing



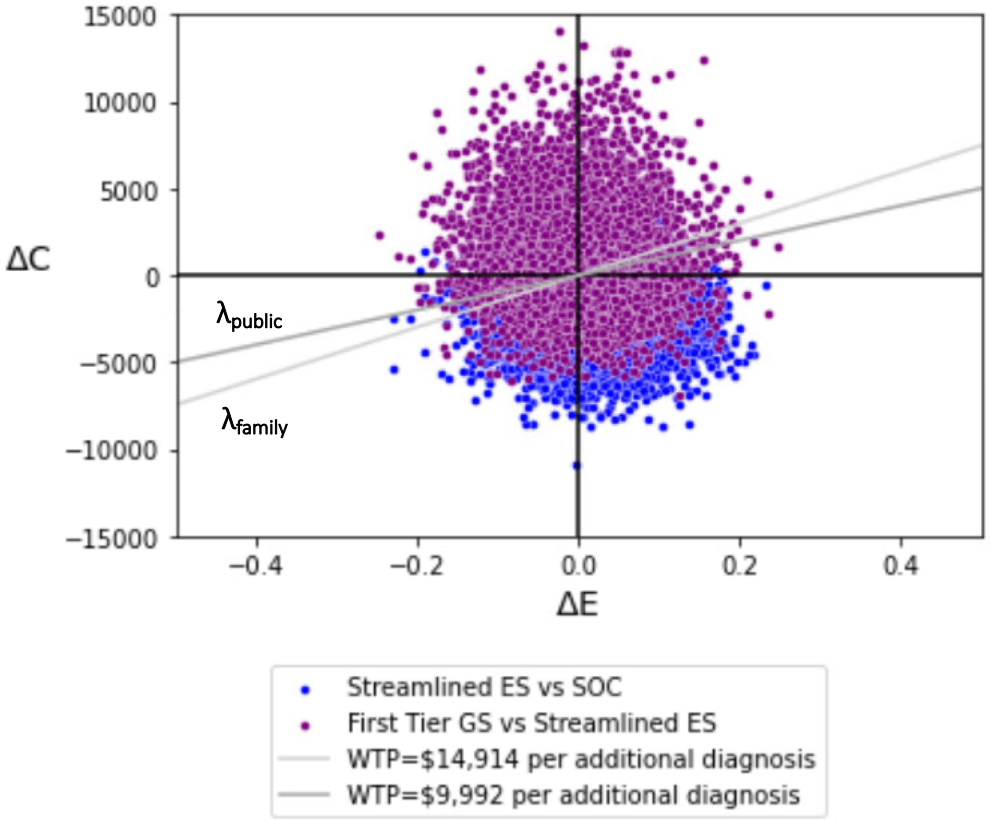
Shorter time to diagnosis for streamlined ES or first-tier GS vs. SOC.

Results: Incremental analysis

	Streamlined ES vs SOC	First-tier GS vs streamlined ES
Δ Costs	$-2,770 (1,818)	$1,543 (2,991)
Δ Dx (per 1000)	18.57 (63.12)	1.11 (66.5)
ICER	Dominant	Not cost-effective
NMB per 1000 pts at public WTP	$2,956 (1,818)	$-1,541 (2,991)
Percentage of simulations that are cost-effective	93% (58% are dominant)	32%**

Dx: diagnosis; NMB: net monetary benefit; WTP : willingness to pay; ES: exome sequencing; SOC: standard of care; GS: genome sequencing

** 26% GS price reduction or 17% improvement in diagnostic yield required



6. Regier DA, et al. Clin Genet. 2009 Jun;75(6):514-21. doi: 10.1111/j.1399-0004.2009.01193.x.

Key findings and evidence gaps

Current policy of last-tier ES in BC is likely inefficient

Streamlined ES access may yield more rapid diagnoses and cost savings

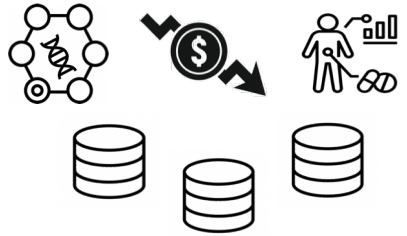
Cost reductions or diagnostic yield improvements required for cost-effective GS

Remaining Gaps

- Prioritization of GS over ES
- Barriers and facilitators for equitable access
- Long-term health and non-health outcomes post-sequencing

Conclusions

Key challenges drive uncertainty in the value of genomic testing for diagnosing rare diseases



Real-world evidence reveals a costly and time-consuming diagnostic odyssey

Earlier-tier GWS is likely cost-effective compared to SOC, although evidence gaps for equitable implementation remain

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