EE171

Time to Diagnosis and Cost Effectiveness of Whole Exome Sequencing (WES) Position in the Diagnostic Pathways of Patients with Suspected Rare Genetic Disease

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Background

- Patients with rare genetic diseases (RGD) often experience a lengthy diagnostic odyssey, involving complex diagnostic testing pathways.
- Whole exome sequencing (WES) has a higher diagnostic yield compared to standard genetic tests and has the potential to reduce time to diagnosis when added early in the pathway.
- There is uncertainty about where in the diagnostic testing pathway a patient with suspected RGD should have a WES test, considering relatively higher cost of a WES.

Objective: To estimate the time-to-diagnosis for patients with RGD and cost-effectiveness of WES testing at different points in the diagnostic pathway.

Methods

- We developed a **discrete event simulation (DES)** model to compare five diagnostic pathways (Figure 1) .
- The standard of care, Tier 2 where WES is the second test after a non-WES test, was compared with the other four strategies.

The model was populated using data on 281 patients (age ≤ 18 years old at WES report date, first indicator test ≥ 2002 April 01) from the SOLVE study, which used retrospective chart reviews of the diagnostic process of patients who received WES as part of their diagnostic journey[1].

- Costs included the costs of indicator (Chromosome micorarray, Gene Panel, Single Gene, WES) and non-indicator tests, he probability of diagnosis, i.e., the probability of getting certain or partial diagnosis was modelled using expert geneticists' estimates.
- The time between events (test results) were modelled using a Log-logistic/Weibull (non-WES tests) and Gompertz/Log-normal mixture distribution (WES tests).
- Patient-level test costs were modelled using empirical distributions.
- Background mortality was modelled using a Gompertz distribution[2].
- Time-to-events and costs (in Canadian dollars) were discounted at 1.5%.
- A probabilistic analysis was performed to quantify parameter uncertainty through 500 non-parametric bootstrap samples and evaluating the simulation model for each sample using simulated 100,000 individuals per strategy

Figure 1. Model structure displaying the 5 testing strategies defined by whether and where WES is used in the diagnostic pathway?

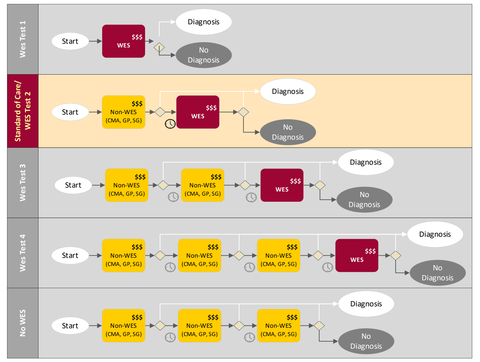
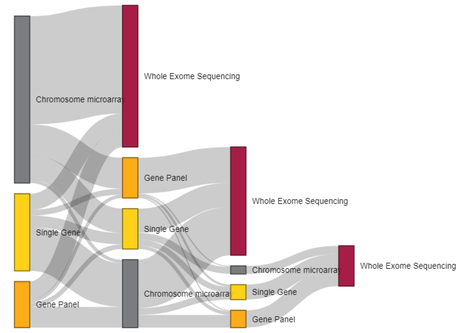
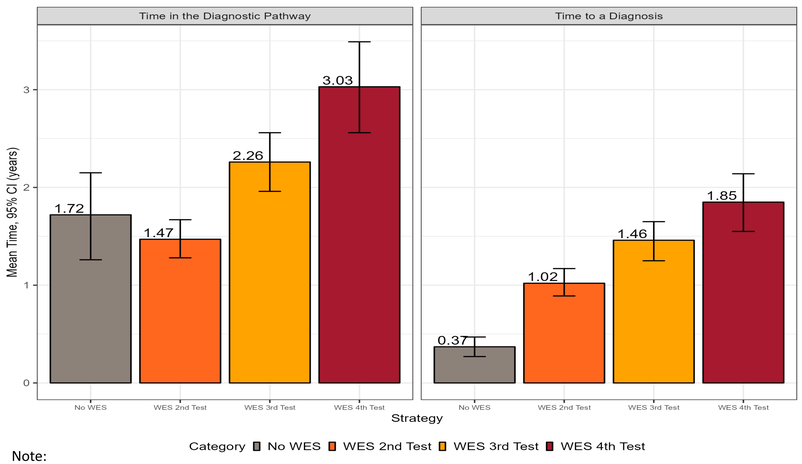


Figure 2. Sankey diagram illustrating the sequence of indicator tests from the SOLVE data.



Results

Figure 3. Average strategy-specific time (in years) in the diagnostic pathway and the time to a diagnosis for the different testing strategies with 95% confidence intervals



Note:
- Results for Tier 1 are note presented, because time zero in the simulation was the reporting of the first test result and Tier 1 considers only 1 test, hence the time in the pathway is zero.
- The time in the diagnostic pathway is the time for **all** patients in the simulation, regardless whether they got a diagnosis or not.
- The time to diagnosis is the time spent in the diagnostic pathway for those patients who obtain a diagnosis.

Figure 4. Probabilistic analysis of costs per patient (mean costs and 95%) and probability of diagnosis grouped by strategy; based on 500 runs of 100K individuals.

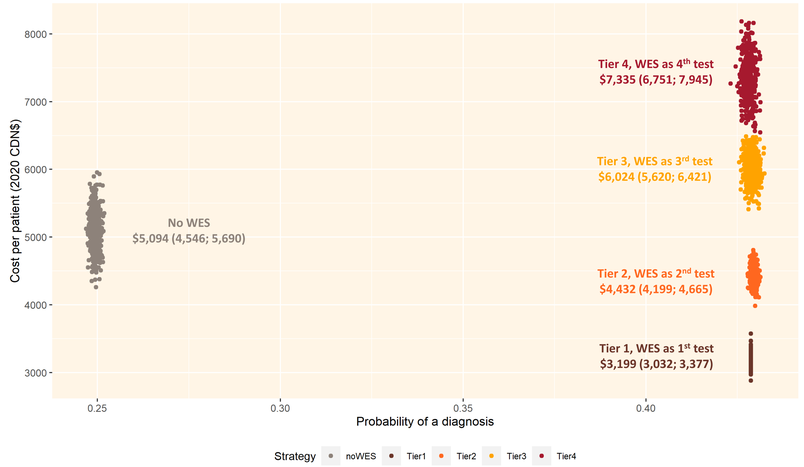


Table 1. Change in average strategy-specific outcomes of the probabilistic analysis for the different testing strategies and diagnostic categories with 95% confidence intervals, with discounted time-to-events and costs (in 2020 Canadian dollars) with **Tier 2, WES as the second test as the comparator**.

Testing strategy	Δ in Incremental Diagnosis	Δ in Time to Diagnosis (years)	Δ in Time in the Diagnostic Pathway (years)	Δ in Incremental Cost per Patient
WES as 1st test	-	-1.02 (-1.17; -0.89)	-1.47 (-1.67; -1.28)	$ -1233.72 (-1415.78; -1063.08)
WES as 3rd test	-	0.43 (0.27; 0.59)	0.79 (0.55; 1.02)	$ 1591.95 (1356.50; 1816.83)
WES as 4th test	-	0.83 (0.53; 1.09)	1.56 (1.11; 1.97)	$ 2902.55 (2481.79; 3370.00)
No WES	-0.18 (-0.18; -0.18)	-0.65 (-0.82; -0.49)	0.25 (-0.24; 0.73)	$ 661.62 (244.69; 1136.00)

Note: "-" indicate a change < - 0.01

Conclusions

These preliminary results from the DES model indicate that introducing WES as the first test in the diagnostic pathway for patients with suspected RGD could:
- decrease the cost, time to a diagnosis and time in the diagnostic pathway.
- increase the probability of receiving a diagnosis from 25%, *with no WES test,* to 43%, *with a WES test*,

Compared to no WES, introducing WES as the first or second test, could decrease the expected time of RGD patients time in the diagnostic pathway by as much as three months (0.25 years) but could increase the time to diagnosis for those with a diagnosis.

Next Steps

- The next phase of the Care for Rare SOLVE study has collected data from ~n=650 patients in Alberta and Ontario which will be linked to post-WES disease management decisions and administrative health data to estimate all direct health care costs associated with the diagnostic pathway.

References:
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3. Gorini, F., Coi, A., Mezzasalma, L. et al. Survival of patients with rare diseases: a population-based study in Tuscany (Italy). Orphanet J Rare Dis 16, 275 (2021). https://doi.org/10.1186/s13023-021-01907-0

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