LONG-TERM HEALTH OUTCOMES OF HUNTINGTON'S DISEASE AND THE IMPACT OF FUTURE DISEASE-MODIFYING TREATMENTS: A US-BASED DECISION MODELING ANALYSIS

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BACKGROUND and OBJECTIVE

- Disease-modifying treatments (DMT) such as gene therapy (GTx) are currently under investigation as a potential treatment for Huntington's disease (HD).
- Once a clinical trial evidence base for HD DMTs is established, decision-analytic modeling will be necessary to assess its long-term health impacts and economic value in various global settings.
- **Our objective was estimation of the long-term natural history of HD progression to explore the potential efficacy impacts and value of a hypothetical DMT using a decision-analytic modeling framework.**

METHODS

- We developed a health state transition model that separately analyzed populations composed of pre-functional decline (PFD, total functional score [TFC] 13), functional decline Shoulson & Fahn category 1 (SF1, TFC 13-11), and functional decline SF2 (TFC 10-7) individuals.[1]
- After validating the long-term progression trajectory of functional decline HD patients using the ENROLL-HD database (version PDS5),[2] three-year outcomes from the published TRACK-HD longitudinal study[3,4] were linearly extrapolated to estimate the long-term health outcomes and costs of each population.
- For PFD individuals, we utilized the HD normalized prognostic index (PIN) to predict the timing of functional decline onset.[5]
- HD costs and quality-adjusted life-years (QALYs) were estimated over a lifetime time horizon by applying health state-specific costs and utilities derived from a related HD burden of illness study.[6,7]
- We then estimated the long-term health impacts of hypothetical HD treatments that (a) delayed onset of functional decline, (b) slowed progression after onset, or (c) combinations of (a) and (b).
- Last, we conducted deterministic and probabilistic sensitivity analyses to assess model uncertainties.

REFERENCES

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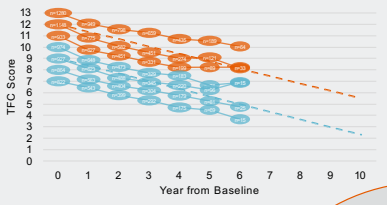
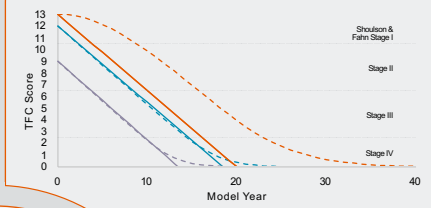
Figure 2. Validation of TRACK-HD Simple Linear Regression vs. ENROLL-HD



Natural History of HD: Dashed lines indicate average TFC Progression for Motor Manifest HD (UHDRS DCL = 4). Simple linear regression extrapolation of TRACK-HD results was used to estimate the natural history of TFC progression. The ovals are the observed means at each visit from ENROLL-HD (with the sample size denoted), used here to validate versus the TRACK-HD regression line.

Figure 3. HD Natural History Modeling for the Three Included Populations



- Dashed lines: simple linear regression based on TRACK-HD
- Solid lines: modeled TFC (weighted average across health states)

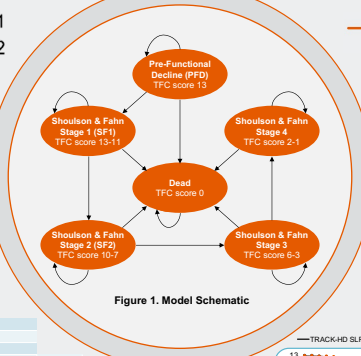


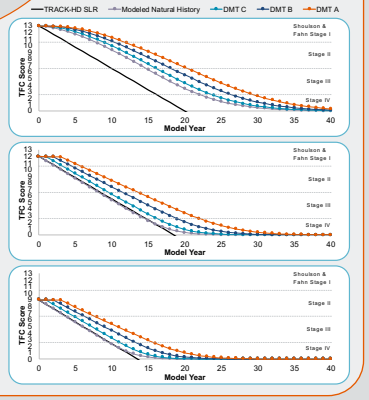
Figure 1. Model Schematic

Table 1. Model Parameters

General Model Settings				
Patient Age (years)	40			
Annual Discount Rate	3%			
Sensitivity Analyses Range % +/-	25%			
Number of Probabilistic Analysis Simulations	5,000			
Pre-Functional Decline & Shoulson & Fahn Stage I				
CAG Repeats	40			
Total Functional Capacity (TFC) Score	13			
Total Motor Score (TMS)	2			
Symbol Digit Modalities Test (SDMT) Score	50			
Parameter	**Value/Delta**	**Lower**	**Upper**	**Source**
Natural History Outcomes for SF1 (TFC 13-11)				
Total Functional Capacity (TFC) Score				
Baseline	12.2			TRACK-HD[3]
12-month Δ	-0.910	-1.360	-0.620	TRACK-HD[3]
36-month Δ	-1.989	correlated		TRACK-HD[4]
Natural History Outcomes for SF2 (TFC 10-7)				
Total Functional Capacity (TFC) Score				
Baseline	8.7			TRACK-HD[3]
12-month Δ	-0.440	-0.780	-0.130	TRACK-HD[3]
36-month Δ	-1.974	correlated		TRACK-HD[4]
Health State Utilities				
Pre-manifest (General Population)	0.86	0.84	0.87	Santana[6]
Shoulson & Fahn I (TFC 13-11)	0.78	0.72	0.85	Santana[6]
Shoulson & Fahn II (TFC 7-10)	0.66	0.59	0.73	Santana[6]
Shoulson & Fahn III (TFC 6-3)	0.54	0.48	0.61	Santana[6]
Shoulson & Fahn IV-V (TFC 0-2)	0.22	0.11	0.32	Santana[6]
Annual Caregiver Costs				
Shoulson & Fahn I (TFC 13-11)	$12,559	$5,098	$20,020	Santana[7]
Shoulson & Fahn II (TFC 10-7)	$15,765	$3,003	$28,527	Santana[7]
Shoulson & Fahn III (TFC 6-3)	$19,233	$4,446	$34,018	Santana[7]
Shoulson & Fahn IV (TFC 2-1)	$43,528	$14,995	$72,720	Santana[7]
Medical Costs				
Shoulson & Fahn I (TFC 13-11)	$0	$0	$0	Santana[7]
Shoulson & Fahn II (TFC 10-7)	$0	$0	$0	Santana
Shoulson & Fahn III (TFC 6-3)	$139,454	$9,616	$269,292	Santana[7]
Shoulson & Fahn IV (TFC 2-1)	$13,541	$4,079	$23,003	Santana[7]

Figure 4. Exploratory Modeling of Hypothetical DMTs

	Delay of functional decline onset (years)	Slowing of disease progression (rate ratio)
DMT A	3	0.75
DMT B	2	0.85
DMT C	1	0.95



RESULTS: NATURAL HISTORY OF HD

	Pre-Functional Decline (TFC 13)		Shoulson & Fahn 1 (TFC 13-11)		Shoulson & Fahn 2 (TFC 10-7)	
Discounted (3%/year) Outcomes	**Base Case**	**95% Credible Range**	**Base Case**	**95% Credible Range**	**Base Case**	**95% Credible Range**
Total Costs	**$681,903**	**($302,182 to $1,129,817)**	**$874,968**	**($386,456 to $1,505,724)**	**$935,277**	**($373,893 to $2,018,083)**
Standard Care	$213,750	($131,434 to $313,592)	$273,346	($167,194 to $414,888)	$246,265	($137,519 to $483,751)
Shoulson & Fahn Stage I	$29,652	($12,186 to $57,178)	$36,998	($14,885 to $72,255)	–	–
Shoulson & Fahn Stage II	$63,682	($16,761 to $126,604)	$80,233	($17,363 to $162,817)	$66,334	($14,975 to $226,705)
Shoulson & Fahn Stage III	$62,062	($16,917 to $110,789)	$79,695	($22,038 to $147,602)	$91,220	($23,151 to $202,450)
Shoulson & Fahn Stage IV	$58,354	($22,151 to $91,911)	$76,420	($30,683 to $121,609)	$88,710	($22,330 to $155,966)
Societal Cost	$468,152	($97,491 to $907,543)	$601,622	($135,737 to $1,190,872)	$689,012	($148,169 to $1,647,992)
Shoulson & Fahn Stage III	$449,999	($83,043 to $891,242)	$577,848	($111,742 to $1,169,136)	$661,416	($129,646 to $1,619,359)
Shoulson & Fahn Stage IV	$18,153	($5,651 to $30,138)	$23,773	($7,726 to $39,886)	$27,597	($5,353 to $50,249)
Total QALYs	**11.50**	**(9.67 to 14.52)**	**8.29**	**(6.35 to 11.92)**	**5.79**	**(4.14 to 13.08)**
Pre-Functional Decline	4.95	(4.46 to 5.75)	–	–	–	–
Shoulson & Fahn Stage I	1.85	(1.34 to 2.91)	2.31	(1.66 to 3.81)	–	–
Shoulson & Fahn Stage II	2.66	(2.01 to 3.72)	3.35	(2.52 to 5.00)	2.77	(1.90 to 8.45)
Shoulson & Fahn Stage III	1.75	(1.39 to 2.08)	2.25	(1.77 to 2.85)	2.57	(1.81 to 4.33)
Shoulson & Fahn Stage IV	0.29	(0.15 to 0.43)	0.38	(0.21 to 0.57)	0.44	(0.20 to 0.72)
Total Life Years	**17.08**	**(14.37 to 21.15)**	**13.93**	**(10.88 to 19.19)**	**10.99**	**(8.28 to 22.15)**

- The lifetime extrapolation for the PFD population resulted in the greatest gains in life years and QALYs, and at the lowest total cost.
- Compared to the PFD population, the SF1 population resulted in fewer expected life years and QALYs and greater total cost.
- The SF2 population had the lowest expected life years and was the costliest.

RESULTS: EXPLORATORY DMT MODELING

- DMTs resulted in gains in life years and QALYs for all three modeled populations, driven by the assumed delay of onset/further progression and the assumed rate ratios applied to the rate of progression once onset began.
- However, while there were potential cost-savings observed in the PFD population, costs tended to be greater in the SF1 and SF2 populations due to prolonged time spent in the more expensive, lower quality of life health states.

TAKEAWAYS

- Our novel HD modeling framework estimates HD progression over a lifetime and the associated costs and QALYs.
- We found that the health benefits of a novel DMT increase as the DMT efficacy increases, however cost-saving potential may be more limited with SF1 and SF2 populations due to prolonged time spent in more expensive, lower quality of life states of health.
- Our approach can be used for future cost-effectiveness models as positive DMT clinical trial evidence becomes available.