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Comment on "Request for Information (RFI) Related to NIST's Assignments Under Sections 4.1, 4.5 and 11 of the Executive Order Concerning Artificial Intelligence" [Docket No. 231218-0309]

Date:

February 2, 2024

By Electronic Delivery To:

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To Whom It May Concern:

Unlearn.AI, Inc. (Unlearn) is submitting these comments in response to the December 21, 2023 Federal Register notice 88 FR 88368.

Unlearn is innovating advanced machine learning (ML) methods to leverage generative artificial intelligence (AI) in forecasting patient health outcomes, starting with the domain of randomized clinical trials (RCTs). We produce a distribution of longitudinal forecasts for individual trial participants (e.g., their "digital twins"), enabling smaller and more efficient clinical trials to bring effective medicines to patients sooner.

We appreciate that the National Institute of Standards and Technology (NIST) is seeking information to assist in carrying out its initiative for evaluating and auditing capabilities relating to AI technologies. As part of our shared goal to ensure the safe, secure, and trustworthy development and use of AI, Unlearn shares technical specification sheets for each of our prognostic AI models that provide details on the model's input and output variables, characteristics of the data used to train the model, and performance. The model used to produce trial participants' digital twins is trained on completed observational studies and historical clinical trials. With the input of an RCT participant's measured characteristics at the beginning of the RCT, the AI model predicts their expected placebo outcome. We have attached one of our spec sheets to showcase an example of responsible AI innovation that encompasses the trustworthiness characteristics defined in NIST's AI Risk Management Framework (RMF), with a focus on model validation, accuracy, and reliability.

NIST's AI RMF defines validation as the "confirmation, through the provision of objective evidence, that the requirements for specific intended use application have been fulfilled." We concur that when evaluating the validity of models, the paramount criteria should be its performance in the context of use. The intended context of use for Unlearn's generative AI model is to incorporate the model's outputs in the design and analysis of RCTs through prognostic covariate adjustment (PROCOVA). Because PROCOVA maintains the advantageous statistical properties of traditional RCT analysis, this method can be considered a risk-free application of implementing AI outputs in the design and analysis of clinical trials. The prognostic scores of individual trial participants provide an optimal adjustment covariate that can enable smaller and more efficient clinical trials, bringing effective medicines to patients sooner. A further description is available in the European Medicines

Agency (EMA)'s qualification opinion for PROCOVA.

In our work within the drug development space, we have noticed a particular challenge with overlapping terminology used to describe metrics for model performance and trustworthiness. For example, the concept of model validation can be applied to two distinct components of the AI model lifecycle: (1) in an ML context to describe a particular validation fold or cross-validation splits of the training data during the process of modeling; or (2) to describe the performance evaluation of a trained and completed AI model with an independent data set (that was not used to train the model). To provide users with a sense of how well the training and validation sets cover their application, Unlearn's technical spec sheets provide the baseline mean, standard deviation, and 5th and 95th percentile for each input in each of the 5 cross-validation folds. Before users apply our models in a clinical trial, performance is tested on held-out independent datasets which had not been used in model training/modeling procedures. It is important to demonstrate that the test set data was acquired in a setting and/or has a population representative of the intended context of use. For example, in Step 1 of PROCOVA (see EMA qualification), the accuracy of the model's performance in a given trial can be assessed by calculating the correlations between placebo outcomes predicted by the generative AI model and the actual outcomes seen in a historical dataset matching that trial's characteristics.

For prospective clinical trials, documentation of the independent evaluation performed in PROCOVA is provided to the appropriate regulatory bodies. Additional documentation that we provide regulators regarding the development, underlying logic, performance, and use of the AI model includes:

- A description of the AI model and the historical data used to train it.
- The parameters of the trained model, any hyperparameters associated with sampling from the model, and the code for inference.
- Analysis of model performance in a similar population.
- Documented SOPs and controls.
- Controlled and monitored secure cloud computing environment with automated version control, metadata, and audit trail.
- The data input into the AI model to generate the predictions used in the clinical trial, along with details on the steps/code used to transform the raw data into the input format.

While we have presented examples from a risk-free context of use for AI model outputs within the area of drug development, this is just one of many approaches that may be valuable in validating models and measuring performance in a given context of use to define relevant success criteria and performance measures tailored to the specific application. Cross-validation

techniques are used to quantify model performance using available data, while external validation is conducted by testing the model on independent datasets or benchmarking against established methods. Model calibration and confidence estimation are used to assess reliability and uncertainty. Seeking input from external experts provides valuable feedback and alternative perspectives. Continuous monitoring of deployed models and performance evaluation reinforce the accuracy, reliability, and applicability of AI/ML models.

Enhancing the trustworthiness of AI systems involves understanding and managing their risks in their intended context of use, and we believe that the information we have provided will serve NIST in its endeavor to advance responsible technical standards for AI development.

Thank you for taking the time to review our comment.

Best regards,

Jess Ross

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ALS DTG Specifications

This document is a technical specification sheet that is intended to provide details on inputs, outputs, and the performance of the DTG on the dataset described herein. All performance measures are dependent on the exact data input to the DTG and therefore past performance is not a guarantee of future performance on a new dataset.

Amyotrophic Lateral Sclerosis Digital Twin Generator 2.6

Amyotrophic Lateral Sclerosis Digital Twin Generator 2.6 (ALS-DTG-2.6) is a Digital Twin Generator (DTG) released on January 11th, 2024. The AI-generated digital twin is a probabilistic representation of potential placebo outcomes for a specific clinical trial participant, given their baseline characteristics. The DTG forecasts future outcomes, and distributions of future outcomes can be used in novel clinical trial designs to make faster and more reliable decisions. For brevity, this spec sheet only describes the 12 month predictive performance.

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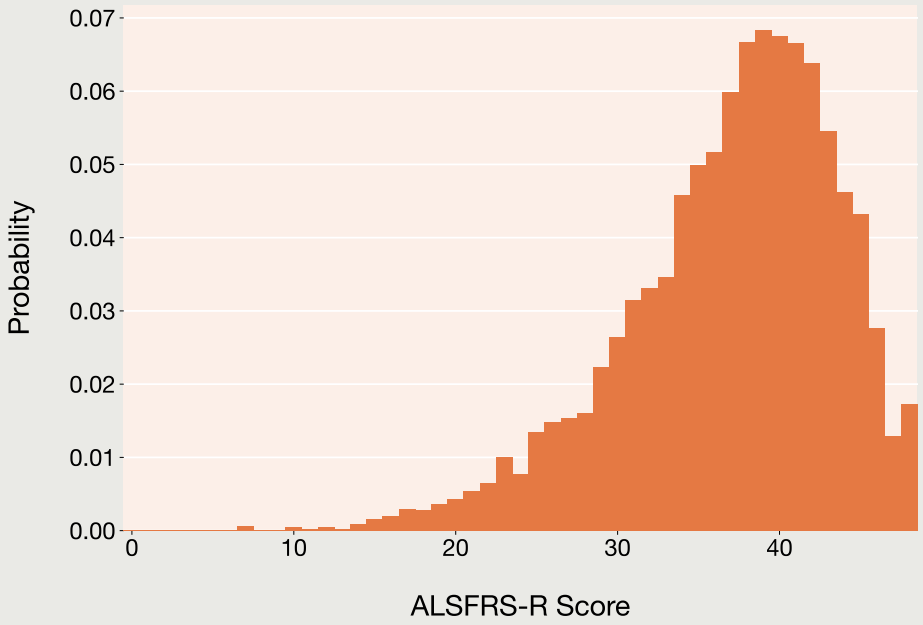
DTG Executive Summary

This section presents a summary of the dataset populations, dataset characteristics, and key performance indicators. For more details on each of these, please refer to later sections in this document. Key characteristics of all participants in the dataset are given in the following table.

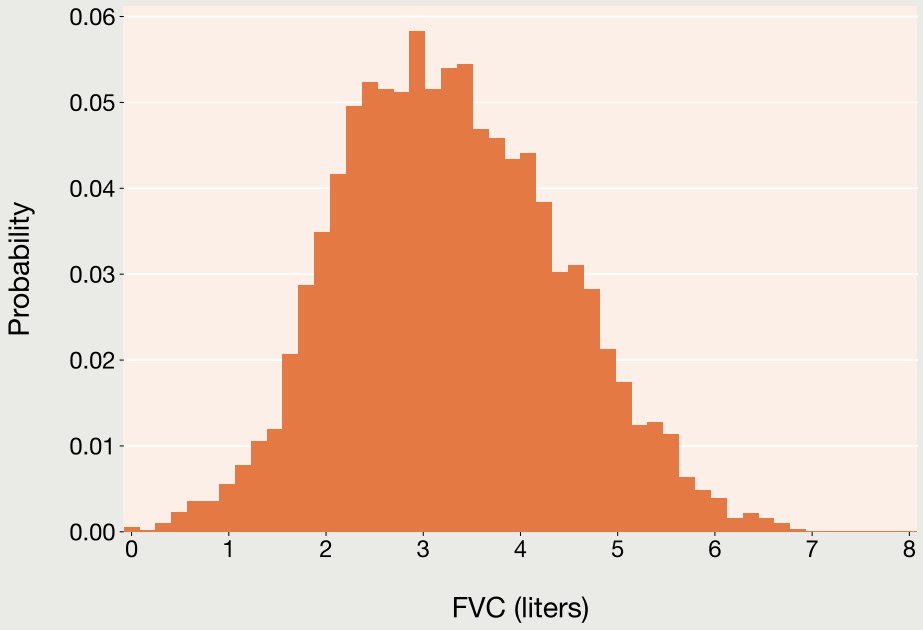
Population Characteristic (n)	**Value**		
Total Population	10,887		
Years of Age (10,680)	57.06 (11.71)		
Symptom Onset in Days (8,910)	-793.26 (877.65)		
FVC Liters (6,195)	3.29 (1.13)		
Sex (10,887)	Female	Male	Not Specified
	38.5%	61.5%	0
Race (9,230)	White	Non-White	Not Specified
	95.1%	4.9%	1,657

The full characterization of the dataset at baseline is given in the DTG Dataset Characterization section. The following figures highlight the full population distribution of key inputs at baseline.

ALSFRS-R Score Baseline Distribution



FVC Baseline Distribution



The full population captured in the dataset includes severity that spans all stages of severity of ALS. This table demonstrates the distribution of different severity subgroups based on the specified inclusion/exclusion criteria.

Population	Definition	Number of Participants
Full Population	All participants in the dataset	10,887
Recent Onset of Symptoms	ALS symptoms recently (within 24 months) developed since baseline measurement	5,739
Minimum Vital Capacity	Cohort has FVC $\geq$ 60% of normal value	3,069

The full performance of the DTG is analyzed in the DTG Performance section. This table highlights the performance of key outputs of the DTG at 12 months [1].

[1]For part of the population, only ALSFRS was measured. We have imputed the three new respiratory components of ALSFRS-R from the respiratory component of ALSFRS. We have verified that imputed total ALSFRS-R scores are accurate on data where both versions are recorded.

Output	**Correlation** Full Population	**Correlation** Recent Onset of Symptoms	**Correlation** Minimum Vital Capacity
ALSFRS-R Score	0.43	0.35	0.40
FVC	0.41	0.41	0.43

DTG Input Requirements

This table provides the complete list of required inputs to the DTG that should be observed at baseline for all participants. Please refer to the section on DTG Performance Sensitivity to understand the impact of completely missing one of these required inputs.

Input Group	Input	Type	Units
ALSFRS-R Components	ALSFRS Climbing	Ordinal	
ALSFRS-R Components	ALSFRS Cutting	Ordinal	
ALSFRS-R Components	ALSFRS Dyspnea	Ordinal	
ALSFRS-R Components	ALSFRS Handwriting	Ordinal	
ALSFRS-R Components	ALSFRS Hygiene	Ordinal	
ALSFRS-R Components	ALSFRS Respiratory Insufficiency	Ordinal	
ALSFRS-R Components	ALSFRS Orthopnea	Ordinal	
ALSFRS-R Components	ALSFRS-R Preslope	Continuous	1/day
ALSFRS-R Components	ALSFRS Salivation	Ordinal	
ALSFRS-R Components	ALSFRS Speech	Ordinal	
ALSFRS-R Components	ALSFRS Swallowing	Ordinal	
ALSFRS-R Components	ALSFRS Turning	Ordinal	
ALSFRS-R Components	ALSFRS Walking	Ordinal	

Input Group	Input	Type	Units
ALSFRS-R Composite Scores	ALSFRS-R Score	Ordinal	
FVC	FVC (liters)	Continuous	L
FVC	FVC Preslope	Continuous	L/day
FVC	FVC (norm)	Continuous	L
SVC	SVC (liters)	Continuous	L
Onset Information	Site of Onset - Bulbar	Binary	
Onset Information	Site of Onset - Limb	Binary	
Onset Information	Site of Onset - Other	Binary	
Onset Information	Symptom Onset Day	Continuous	days
Medications	Taking Amitriptyline	Binary	
Medications	Taking Baclofen	Binary	
Medications	Taking Riluzole	Binary	
Demographics	Age	Continuous	years
Demographics	Caucasian Race	Binary	
Demographics	Sex	Binary	
Labs & Vitals	Alanine Aminotransferase	Continuous	U/L
Labs & Vitals	Albumin	Continuous	g/L
Labs & Vitals	Alkaline Phosphatase	Continuous	U/L
Labs & Vitals	Aspartate Aminotransferase	Continuous	U/L

Input Group	Input	Type	Units
Labs & Vitals	Basophils	Continuous	giga/L
Labs & Vitals	Blood Urea Nitrogen	Continuous	mmol/L
Labs & Vitals	Calcium	Continuous	mmol/L
Labs & Vitals	Chloride	Continuous	mmol/L
Labs & Vitals	Cholesterol	Continuous	mmol/L
Labs & Vitals	Creatine Kinase	Continuous	U/L
Labs & Vitals	Creatinine	Continuous	mg/dL
Labs & Vitals	Diastolic Blood Pressure	Continuous	mmHg
Labs & Vitals	Eosinophils	Continuous	giga/L
Labs & Vitals	Gamma Glutamyl Transferase	Continuous	U/L
Labs & Vitals	Glucose	Continuous	mmol/L
Labs & Vitals	Heart Rate	Continuous	bpm
Labs & Vitals	Height	Continuous	cm
Labs & Vitals	Hematocrit	Continuous	%
Labs & Vitals	Hemoglobin	Continuous	g/L
Labs & Vitals	Hemoglobin A1c	Continuous	%
Labs & Vitals	Lactate Dehydrogenase	Continuous	U/L
Labs & Vitals	Lymphocytes	Continuous	giga/L
Labs & Vitals	Monocytes	Continuous	giga/L

Input Group	Input	Type	Units
Labs & Vitals	Neutrophils	Continuous	giga/L
Labs & Vitals	Phosphorus	Continuous	mg/dL
Labs & Vitals	Plasma Neurofilament Light (NfL)	Continuous	pg/mL
Labs & Vitals	Platelet	Continuous	giga/L
Labs & Vitals	Potassium	Continuous	mmol/L
Labs & Vitals	Protein	Continuous	g/L
Labs & Vitals	Respiratory Rate	Continuous	breaths/min
Labs & Vitals	Sodium	Continuous	mmol/L
Labs & Vitals	Systolic Blood Pressure	Continuous	mmHg
Labs & Vitals	Temperature	Continuous	celsius
Labs & Vitals	Total Bilirubin	Continuous	mg/dL
Labs & Vitals	Triglycerides	Continuous	g/L
Labs & Vitals	Uric Acid	Continuous	mg/dL
Labs & Vitals	Weight	Continuous	kg
Medical History	ALS Diagnosis Definite	Binary	
Medical History	ALS Diagnosis Possible	Binary	
Medical History	ALS Diagnosis Probable	Binary	
Medical History	ALS Diagnosis Probable (Laboratory Supported)	Binary	
Medical History	ALS Diagnosis Suspected	Binary	

DTG Dataset Characterization

The DTGs are capable of producing predictions at any time post baseline, but the typical data available for testing is collected at a 3 month cadence out to 12, 18, or 24 months depending on the clinical trial design. The DTGs are trained on data that has been collected from a variety of sources and harmonized into one single dataset. This single dataset is then split into 5 cross validation (CV) folds. The final DTG consists of an ensemble of 5 DTGs which have each been trained with a different cross validation fold left out.

The following table presents detailed characteristics of the required inputs at baseline. For every cross validation fold, the baseline mean, standard deviation (in parentheses), and 5th and 95th percentile (in brackets) are presented for each input.

Baseline Input	**Units**	**CV 1** Mean (Std) [5%, 95%]	**CV 2** Mean (Std) [5%, 95%]	**CV 3** Mean (Std) [5%, 95%]	**CV 4** Mean (Std) [5%, 95%]	**CV 5** Mean (Std) [5%, 95%]
ALSFRS Climbing		2.04 (1.44) [0.00, 4.00]	2.02 (1.45) [0.00, 4.00]	1.98 (1.44) [0.00, 4.00]	1.95 (1.43) [0.00, 4.00]	1.89 (1.43) [0.00, 4.00]
ALSFRS Cutting		2.70 (1.20) [1.00, 4.00]	2.67 (1.20) [0.00, 4.00]	2.71 (1.19) [1.00, 4.00]	2.72 (1.20) [1.00, 4.00]	2.67 (1.23) [0.00, 4.00]

Baseline Input	Units	CV 1 Mean (Std) [5%, 95%]	CV 2 Mean (Std) [5%, 95%]	CV 3 Mean (Std) [5%, 95%]	CV 4 Mean (Std) [5%, 95%]	CV 5 Mean (Std) [5%, 95%]
ALSFRS Dyspnea		3.55 (0.81) [2.00, 4.00]	3.49 (0.85) [2.00, 4.00]	3.49 (0.87) [2.00, 4.00]	3.51 (0.82) [2.00, 4.00]	3.46 (0.88) [2.00, 4.00]
ALSFRS Handwriting		2.97 (1.04) [1.00, 4.00]	2.95 (1.07) [0.00, 4.00]	2.94 (1.07) [0.00, 4.00]	2.98 (1.06) [0.00, 4.00]	2.93 (1.10) [0.00, 4.00]
ALSFRS Hygiene		2.56 (1.07) [1.00, 4.00]	2.52 (1.07) [0.00, 4.00]	2.51 (1.07) [1.00, 4.00]	2.55 (1.06) [1.00, 4.00]	2.49 (1.10) [0.00, 4.00]
ALSFRS Respiratory Insufficiency		3.86 (0.50) [2.00, 4.00]	3.85 (0.51) [2.00, 4.00]	3.84 (0.52) [2.00, 4.00]	3.82 (0.56) [2.00, 4.00]	3.81 (0.58) [2.00, 4.00]
ALSFRS Orthopnea		3.74 (0.71) [2.00, 4.00]	3.69 (0.78) [2.00, 4.00]	3.68 (0.79) [2.00, 4.00]	3.68 (0.78) [2.00, 4.00]	3.68 (0.81) [2.00, 4.00]
ALSFRS-R Preslope	1/day	-0.02 (0.02) [-0.05, -0.00]	-0.02 (0.03) [-0.06, -0.00]	-0.02 (0.02) [-0.05, -0.00]	-0.02 (0.02) [-0.05, -0.00]	-0.02 (0.02) [-0.06, -0.00]
ALSFRS Salivation		3.41 (0.91) [1.00, 4.00]	3.42 (0.91) [2.00, 4.00]	3.40 (0.92) [1.00, 4.00]	3.38 (0.93) [2.00, 4.00]	3.42 (0.90) [2.00, 4.00]
ALSFRS Speech		3.18 (1.03) [1.00, 4.00]	3.20 (1.05) [1.00, 4.00]	3.15 (1.07) [1.00, 4.00]	3.11 (1.05) [1.00, 4.00]	3.16 (1.02) [1.00, 4.00]
ALSFRS Swallowing		3.47 (0.80) [2.00, 4.00]	3.45 (0.81) [2.00, 4.00]	3.44 (0.81) [2.00, 4.00]	3.41 (0.83) [2.00, 4.00]	3.44 (0.81) [2.00, 4.00]

Baseline Input	Units	CV 1 Mean (Std) [5%, 95%]	CV 2 Mean (Std) [5%, 95%]	CV 3 Mean (Std) [5%, 95%]	CV 4 Mean (Std) [5%, 95%]	CV 5 Mean (Std) [5%, 95%]
ALSFRS Turning		3.03 (0.98) [1.00, 4.00]	3.01 (1.00) [1.00, 4.00]	3.02 (1.00) [1.00, 4.00]	3.08 (0.98) [1.00, 4.00]	2.99 (1.03) [1.00, 4.00]
ALSFRS Walking		2.70 (0.99) [1.00, 4.00]	2.68 (1.00) [1.00, 4.00]	2.69 (0.99) [1.00, 4.00]	2.72 (0.96) [1.00, 4.00]	2.65 (1.01) [1.00, 4.00]
ALSFRS-R Score		37.19 (6.53) [24.00, 46.00]	36.96 (6.59) [25.00, 46.00]	36.81 (6.63) [25.00, 45.00]	36.95 (6.58) [25.00, 46.00]	36.71 (6.82) [23.00, 46.00]
FVC (liters)	L	3.30 (1.10) [1.66, 5.19]	3.31 (1.15) [1.58, 5.33]	3.25 (1.13) [1.54, 5.15]	3.31 (1.14) [1.49, 5.29]	3.28 (1.11) [1.59, 5.17]
FVC Preslope	L/day	-0.00 (0.00) [-0.01, -0.00]	-0.00 (0.00) [-0.01, -0.00]	-0.00 (0.00) [-0.01, -0.00]	-0.00 (0.00) [-0.01, -0.00]	-0.00 (0.00) [-0.01, -0.00]
FVC (norm)	L	4.20 (0.92) [2.78, 5.67]	4.17 (0.94) [2.72, 5.65]	4.18 (0.92) [2.76, 5.69]	4.18 (0.92) [2.70, 5.63]	4.22 (0.93) [2.78, 5.69]
SVC (liters)	L	3.48 (1.05) [1.84, 5.40]	3.43 (1.06) [2.00, 5.03]	3.37 (1.02) [1.81, 5.00]	3.56 (1.04) [1.92, 5.13]	3.46 (1.09) [1.93, 5.23]
Site of Onset - Bulbar		0.22 (0.42) [0.00, 1.00]	0.21 (0.41) [0.00, 1.00]	0.22 (0.42) [0.00, 1.00]	0.22 (0.41) [0.00, 1.00]	0.24 (0.43) [0.00, 1.00]
Site of Onset - Limb		0.71 (0.45) [0.00, 1.00]	0.72 (0.45) [0.00, 1.00]	0.72 (0.45) [0.00, 1.00]	0.72 (0.45) [0.00, 1.00]	0.70 (0.46) [0.00, 1.00]

Baseline Input	**Units**	**CV 1** Mean (Std) [5%, 95%]	**CV 2** Mean (Std) [5%, 95%]	**CV 3** Mean (Std) [5%, 95%]	**CV 4** Mean (Std) [5%, 95%]	**CV 5** Mean (Std) [5%, 95%]
Site of Onset - Other		0.06 (0.24) [0.00, 1.00]	0.07 (0.25) [0.00, 1.00]	0.06 (0.24) [0.00, 1.00]	0.07 (0.25) [0.00, 1.00]	0.06 (0.24) [0.00, 1.00]
Symptom Onset Day	days	-800.27 (855.68) [-1889.35, -208.15]	-759.91 (845.42) [-1774.55, -202.00]	-817.95 (779.19) [-1928.05, -207.65]	-831.65 (1092.04) [-1989.40, -208.20]	-759.37 (793.22) [-1814.20, -195.00]
Taking Amitriptyline		0.04 (0.20) [0.00, 0.00]	0.05 (0.22) [0.00, 1.00]	0.04 (0.21) [0.00, 0.00]	0.05 (0.21) [0.00, 0.00]	0.04 (0.20) [0.00, 0.00]
Taking Baclofen		0.11 (0.31) [0.00, 1.00]	0.10 (0.30) [0.00, 1.00]	0.11 (0.31) [0.00, 1.00]	0.11 (0.32) [0.00, 1.00]	0.10 (0.30) [0.00, 1.00]
Taking Riluzole		0.48 (0.50) [0.00, 1.00]	0.48 (0.50) [0.00, 1.00]	0.47 (0.50) [0.00, 1.00]	0.47 (0.50) [0.00, 1.00]	0.50 (0.50) [0.00, 1.00]
Age	years	56.87 (11.73) [36.00, 74.00]	57.27 (11.76) [37.00, 74.20]	57.44 (11.56) [36.00, 74.00]	56.78 (11.64) [36.00, 73.00]	56.93 (11.83) [35.00, 74.00]
Caucasian Race		0.94 (0.23) [0.00, 1.00]	0.95 (0.21) [1.00, 1.00]	0.95 (0.22) [1.00, 1.00]	0.95 (0.23) [0.00, 1.00]	0.96 (0.19) [1.00, 1.00]
Sex		0.39 (0.49) [0.00, 1.00]	0.38 (0.49) [0.00, 1.00]	0.39 (0.49) [0.00, 1.00]	0.38 (0.49) [0.00, 1.00]	0.38 (0.49) [0.00, 1.00]
Alanine Aminotransferase	U/L	33.41 (20.52) [13.00, 66.00]	34.25 (19.71) [13.00, 70.15]	32.40 (16.73) [13.00, 64.00]	33.96 (19.86) [13.00, 70.00]	33.11 (18.51) [12.00, 67.95]

Baseline Input	Units	CV 1 Mean (Std) [5%, 95%]	CV 2 Mean (Std) [5%, 95%]	CV 3 Mean (Std) [5%, 95%]	CV 4 Mean (Std) [5%, 95%]	CV 5 Mean (Std) [5%, 95%]
Albumin	g/L	43.69 (3.23) [39.00, 49.00]	43.50 (3.24) [38.00, 48.50]	43.27 (3.40) [37.08, 49.00]	43.44 (3.25) [38.00, 49.00]	43.48 (3.32) [38.00, 48.50]
Alkaline Phosphatase	U/L	73.87 (24.13) [43.70, 114.00]	75.26 (25.63) [44.00, 121.40]	74.85 (24.92) [45.00, 119.00]	75.61 (27.19) [44.00, 119.00]	74.88 (25.44) [44.00, 118.00]
Aspartate Aminotransferase	U/L	29.41 (19.36) [15.00, 50.00]	29.53 (11.92) [15.00, 51.00]	28.68 (11.48) [14.00, 51.00]	29.31 (12.30) [15.00, 51.00]	28.91 (11.42) [14.88, 51.00]
Basophils	giga/L	0.04 (0.03) [0.00, 0.10]	0.04 (0.07) [0.00, 0.10]	0.04 (0.04) [0.00, 0.10]	0.04 (0.03) [0.00, 0.10]	0.04 (0.04) [0.00, 0.10]
Blood Urea Nitrogen	mmol/L	5.42 (1.69) [3.20, 8.35]	5.61 (1.80) [3.29, 8.93]	5.54 (1.78) [3.21, 8.57]	5.52 (1.71) [3.21, 8.40]	5.62 (1.75) [3.26, 8.51]
Calcium	mmol/L	2.36 (0.12) [2.17, 2.55]	2.36 (0.12) [2.20, 2.55]	2.36 (0.12) [2.17, 2.55]	2.35 (0.12) [2.17, 2.55]	2.36 (0.11) [2.20, 2.55]
Chloride	mmol/L	102.75 (3.22) [97.00, 108.00]	102.64 (3.36) [97.00, 108.00]	102.46 (3.30) [97.00, 107.00]	102.64 (3.42) [97.00, 108.00]	102.80 (3.26) [97.42, 108.00]
Cholesterol	mmol/L	5.78 (1.14) [4.01, 7.74]	5.78 (1.08) [4.14, 7.74]	5.79 (1.12) [4.14, 7.69]	5.86 (1.17) [3.98, 7.88]	5.85 (1.11) [4.22, 7.79]
Creatine Kinase	U/L	253.93 (232.51) [49.00, 653.40]	278.29 (236.66) [53.35, 790.95]	273.39 (242.46) [50.20, 744.80]	284.66 (255.88) [51.00, 763.45]	276.07 (250.53) [50.20, 788.40]

Baseline Input	Units	CV 1 Mean (Std) [5%, 95%]	CV 2 Mean (Std) [5%, 95%]	CV 3 Mean (Std) [5%, 95%]	CV 4 Mean (Std) [5%, 95%]	CV 5 Mean (Std) [5%, 95%]
Creatinine	mg/dL	0.79 (0.22) [0.50, 1.14]	0.80 (0.22) [0.48, 1.15]	0.79 (0.21) [0.48, 1.11]	0.80 (0.20) [0.50, 1.10]	0.79 (0.21) [0.48, 1.12]
Diastolic Blood Pressure	mmHg	80.14 (10.44) [62.00, 97.00]	80.47 (10.52) [62.00, 98.40]	80.43 (10.68) [62.00, 99.00]	80.25 (10.38) [62.00, 97.95]	80.56 (10.53) [62.00, 98.00]
Eosinophils	giga/L	0.38 (0.76) [0.04, 2.00]	0.35 (0.74) [0.04, 2.00]	0.42 (0.81) [0.04, 2.00]	0.36 (0.64) [0.04, 2.00]	0.37 (0.88) [0.04, 2.00]
Gamma Glutamyl Transferase	U/L	34.76 (53.60) [10.33, 81.35]	33.72 (38.84) [11.00, 79.60]	34.02 (36.51) [10.55, 80.75]	35.71 (37.08) [11.00, 91.00]	34.57 (30.21) [11.45, 86.55]
Glucose	mmol/L	5.40 (1.23) [4.16, 7.44]	5.38 (1.43) [4.05, 7.49]	5.37 (1.27) [4.11, 7.30]	5.43 (1.35) [4.10, 7.44]	5.36 (1.28) [4.10, 7.13]
Heart Rate	bpm	76.41 (12.48) [59.00, 98.00]	76.42 (12.23) [60.00, 98.00]	76.25 (12.27) [58.00, 99.00]	75.94 (11.97) [60.00, 98.00]	75.69 (12.37) [58.00, 97.00]
Height	cm	170.81 (9.95) [154.90, 186.00]	170.72 (10.16) [154.00, 187.53]	170.98 (9.76) [155.00, 187.96]	171.03 (9.79) [154.94, 186.00]	171.27 (10.04) [155.00, 187.96]
Hematocrit	%	43.02 (3.87) [36.50, 49.00]	43.25 (3.85) [37.00, 49.46]	43.06 (3.78) [37.00, 49.00]	43.24 (3.80) [37.00, 49.50]	43.41 (3.87) [37.20, 49.80]
Hemoglobin	g/L	144.61 (13.74) [122.00, 165.00]	144.81 (14.07) [122.00, 165.00]	144.57 (12.80) [123.00, 164.80]	144.88 (13.17) [125.00, 166.00]	145.35 (13.50) [124.00, 166.00]

Baseline Input	Units	CV 1 Mean (Std) [5%, 95%]	CV 2 Mean (Std) [5%, 95%]	CV 3 Mean (Std) [5%, 95%]	CV 4 Mean (Std) [5%, 95%]	CV 5 Mean (Std) [5%, 95%]
Hemoglobin A1c	%	5.38 (0.79) [4.30, 6.40]	5.42 (0.69) [4.45, 6.40]	5.42 (0.80) [4.43, 6.60]	5.37 (0.72) [4.40, 6.50]	5.39 (0.78) [4.40, 6.43]
Lactate Dehydrogenase	U/L	184.41 (67.46) [122.05, 263.95]	182.85 (58.25) [125.00, 259.30]	182.39 (47.40) [124.75, 261.00]	179.04 (54.40) [121.00, 249.75]	179.11 (59.99) [120.80, 252.00]
Lymphocytes	giga/L	1.78 (0.57) [0.97, 2.86]	1.79 (0.63) [0.96, 3.00]	1.82 (0.67) [0.98, 2.92]	1.80 (0.66) [0.96, 2.92]	1.75 (0.59) [0.98, 2.74]
Monocytes	giga/L	0.43 (0.18) [0.19, 0.73]	0.43 (0.17) [0.20, 0.75]	0.43 (0.17) [0.20, 0.75]	0.43 (0.16) [0.20, 0.73]	0.43 (0.18) [0.19, 0.74]
Neutrophils	giga/L	4.34 (1.56) [2.16, 7.15]	4.48 (1.49) [2.49, 7.13]	4.39 (1.57) [2.23, 7.23]	4.34 (1.58) [2.49, 7.02]	4.36 (1.41) [2.42, 6.76]
Phosphorus	mg/dL	3.70 (0.48) [2.91, 4.50]	3.70 (0.46) [3.00, 4.49]	3.68 (0.46) [2.90, 4.41]	3.70 (0.48) [2.90, 4.50]	3.70 (0.47) [2.90, 4.49]
Plasma Neurofilament Light (NfL)	pg/mL	—	—	—	70.30 (36.71) [19.90, 125.95]	162.99 (146.09) [42.40, 390.20]
Platelet	giga/L	249.76 (62.28) [160.22, 355.55]	246.06 (59.47) [160.80, 352.00]	249.04 (63.09) [157.40, 356.60]	249.19 (61.64) [161.55, 355.45]	249.40 (62.29) [160.65, 359.35]
Potassium	mmol/L	4.19 (0.34) [3.70, 4.80]	4.20 (0.37) [3.60, 4.80]	4.21 (0.39) [3.70, 4.80]	4.20 (0.35) [3.70, 4.80]	4.22 (0.41) [3.70, 4.80]

Baseline Input	**Units**	**CV 1** Mean (Std) [5%, 95%]	**CV 2** Mean (Std) [5%, 95%]	**CV 3** Mean (Std) [5%, 95%]	**CV 4** Mean (Std) [5%, 95%]	**CV 5** Mean (Std) [5%, 95%]
Protein	g/L	72.30 (4.83) [65.00, 80.00]	72.12 (4.63) [65.00, 79.50]	72.03 (4.90) [64.00, 80.00]	72.10 (4.65) [65.00, 80.00]	72.10 (4.72) [65.00, 80.00]
Respiratory Rate	breaths/min	17.61 (3.18) [12.00, 24.00]	17.54 (3.37) [12.00, 24.00]	17.56 (3.51) [12.00, 24.00]	17.65 (3.56) [12.00, 24.00]	17.44 (3.48) [12.00, 24.00]
Sodium	mmol/L	140.25 (2.55) [136.00, 144.70]	140.25 (2.69) [136.00, 145.00]	140.15 (2.81) [136.00, 144.00]	140.20 (2.66) [136.00, 144.00]	140.29 (2.52) [136.00, 144.00]
Systolic Blood Pressure	mmHg	131.32 (16.83) [108.00, 160.00]	131.85 (16.98) [108.00, 160.00]	131.89 (17.20) [108.00, 160.90]	131.53 (16.74) [108.00, 160.00]	131.64 (16.59) [107.00, 160.00]
Temperature	celsius	36.57 (0.48) [35.80, 37.20]	36.60 (0.53) [35.70, 37.30]	36.58 (0.44) [35.80, 37.22]	36.58 (0.48) [35.84, 37.28]	36.63 (0.44) [35.90, 37.30]
Total Bilirubin	mg/dL	0.62 (0.35) [0.30, 1.20]	0.62 (0.28) [0.30, 1.20]	0.62 (0.30) [0.30, 1.11]	0.61 (0.29) [0.30, 1.10]	0.62 (0.28) [0.30, 1.11]
Triglycerides	g/L	1.67 (1.13) [0.63, 3.67]	1.70 (1.08) [0.66, 3.66]	1.71 (1.20) [0.59, 3.58]	1.72 (1.23) [0.65, 3.76]	1.70 (1.05) [0.69, 3.57]
Uric Acid	mg/dL	291.98 (84.00) [169.48, 431.30]	300.53 (82.50) [178.44, 434.70]	291.99 (80.03) [166.86, 422.31]	296.99 (77.31) [179.38, 428.10]	291.86 (86.68) [160.00, 433.20]
Weight	kg	77.02 (16.47) [52.60, 105.20]	77.07 (16.91) [52.00, 107.00]	76.90 (16.33) [52.20, 106.81]	76.48 (16.42) [52.27, 104.83]	76.39 (16.85) [51.19, 105.00]

Baseline Input	**Units**	**CV 1** Mean (Std) [5%, 95%]	**CV 2** Mean (Std) [5%, 95%]	**CV 3** Mean (Std) [5%, 95%]	**CV 4** Mean (Std) [5%, 95%]	**CV 5** Mean (Std) [5%, 95%]
ALS Diagnosis Definite		0.34 (0.47) [0.00, 1.00]	0.36 (0.48) [0.00, 1.00]	0.35 (0.48) [0.00, 1.00]	0.34 (0.48) [0.00, 1.00]	0.37 (0.48) [0.00, 1.00]
ALS Diagnosis Possible		0.06 (0.25) [0.00, 1.00]	0.10 (0.29) [0.00, 1.00]	0.10 (0.30) [0.00, 1.00]	0.08 (0.28) [0.00, 1.00]	0.09 (0.29) [0.00, 1.00]
ALS Diagnosis Probable		0.37 (0.48) [0.00, 1.00]	0.30 (0.46) [0.00, 1.00]	0.33 (0.47) [0.00, 1.00]	0.33 (0.47) [0.00, 1.00]	0.31 (0.46) [0.00, 1.00]
ALS Diagnosis Probable (Laboratory Supported)		0.19 (0.39) [0.00, 1.00]	0.21 (0.41) [0.00, 1.00]	0.18 (0.39) [0.00, 1.00]	0.20 (0.40) [0.00, 1.00]	0.19 (0.39) [0.00, 1.00]
ALS Diagnosis Suspected		0.03 (0.18) [0.00, 0.00]	0.03 (0.18) [0.00, 0.00]	0.04 (0.18) [0.00, 0.00]	0.04 (0.20) [0.00, 0.00]	0.04 (0.19) [0.00, 0.00]

DTG Outputs

This table presents the component level outputs of the DTG. These components can be combined together into composite scores which are described in the DTG Output Composites section. All outputs are predicted for all of the desired longitudinal time points of interest.

Output Group	Output	Units
ALSFRS-R Components	ALSFRS Climbing	
ALSFRS-R Components	ALSFRS Cutting	
ALSFRS-R Components	ALSFRS Dyspnea	
ALSFRS-R Components	ALSFRS Handwriting	
ALSFRS-R Components	ALSFRS Hygiene	
ALSFRS-R Components	ALSFRS Respiratory Insufficiency	
ALSFRS-R Components	ALSFRS Orthopnea	
ALSFRS-R Components	ALSFRS Salivation	
ALSFRS-R Components	ALSFRS Speech	
ALSFRS-R Components	ALSFRS Swallowing	
ALSFRS-R Components	ALSFRS Turning	
ALSFRS-R Components	ALSFRS Walking	
FVC	FVC (liters)	L

Output Group	Output	Units
SVC	SVC (liters)	L
Labs & Vitals	Alanine Aminotransferase	U/L
Labs & Vitals	Albumin	g/L
Labs & Vitals	Alkaline Phosphatase	U/L
Labs & Vitals	Aspartate Aminotransferase	U/L
Labs & Vitals	Basophils	giga/L
Labs & Vitals	Blood Urea Nitrogen	mmol/L
Labs & Vitals	Calcium	mmol/L
Labs & Vitals	Chloride	mmol/L
Labs & Vitals	Cholesterol	mmol/L
Labs & Vitals	Creatine Kinase	U/L
Labs & Vitals	Creatinine	mg/dL
Labs & Vitals	Diastolic Blood Pressure	mmHg
Labs & Vitals	Eosinophils	giga/L
Labs & Vitals	Gamma Glutamyl Transferase	U/L
Labs & Vitals	Glucose	mmol/L
Labs & Vitals	Heart Rate	bpm
Labs & Vitals	Hematocrit	%
Labs & Vitals	Hemoglobin	g/L

Output Group	Output	Units
Labs & Vitals	Hemoglobin A1c	%
Labs & Vitals	Lactate Dehydrogenase	U/L
Labs & Vitals	Lymphocytes	giga/L
Labs & Vitals	Monocytes	giga/L
Labs & Vitals	Neutrophils	giga/L
Labs & Vitals	Phosphorus	mg/dL
Labs & Vitals	Plasma Neurofilament Light (NfL)	pg/mL
Labs & Vitals	Platelet	giga/L
Labs & Vitals	Potassium	mmol/L
Labs & Vitals	Protein	g/L
Labs & Vitals	Respiratory Rate	breaths/min
Labs & Vitals	Sodium	mmol/L
Labs & Vitals	Systolic Blood Pressure	mmHg
Labs & Vitals	Temperature	celsius
Labs & Vitals	Total Bilirubin	mg/dL
Labs & Vitals	Triglycerides	g/L
Labs & Vitals	Uric Acid	mg/dL
Labs & Vitals	Weight	kg
Key Events	Death	days

DTG Output Composites

This table lists common composite scores that can be derived by combining together the component level outputs of the DTG.

Output Composites
ALSFRS-R Score
ALSFRS-R Respiratory Score
ALSFRS-R Gross Motor Score
ALSFRS-R Fine Motor Score
ALSFRS-R Bulbar Score

DTG Performance

This section analyzes the performance of the DTG. The DTG produces distributions of outcomes that are difficult to summarize into a few key metrics, but these tables focus on one of the most important measures which is the correlation of change from baseline at 12 months.

This table contains the performance of all the component level outputs from the DTG as measured on the population described in the DTG Dataset Characterization section.

Output Group	Output	Correlation
ALSFRS-R Components	ALSFRS Climbing	0.58
ALSFRS-R Components	ALSFRS Cutting	0.44
ALSFRS-R Components	ALSFRS Dyspnea	0.37
ALSFRS-R Components	ALSFRS Handwriting	0.46
ALSFRS-R Components	ALSFRS Hygiene	0.45
ALSFRS-R Components	ALSFRS Respiratory Insufficiency	0.31
ALSFRS-R Components	ALSFRS Orthopnea	0.37
ALSFRS-R Components	ALSFRS Salivation	0.43
ALSFRS-R Components	ALSFRS Speech	0.43

Output Group	Output	Correlation
ALSFRS-R Components	ALSFRS Swallowing	0.43
ALSFRS-R Components	ALSFRS Turning	0.42
ALSFRS-R Components	ALSFRS Walking	0.41
FVC	FVC (liters)	0.41
SVC	SVC (liters)	0.45
Labs & Vitals	Alanine Aminotransferase	0.41
Labs & Vitals	Albumin	0.41
Labs & Vitals	Alkaline Phosphatase	0.21
Labs & Vitals	Aspartate Aminotransferase	0.59
Labs & Vitals	Basophils	0.59
Labs & Vitals	Blood Urea Nitrogen	0.45
Labs & Vitals	Calcium	0.55
Labs & Vitals	Chloride	0.48
Labs & Vitals	Cholesterol	0.35
Labs & Vitals	Creatine Kinase	0.50
Labs & Vitals	Creatinine	0.35
Labs & Vitals	Diastolic Blood Pressure	0.48
Labs & Vitals	Eosinophils	0.13
Labs & Vitals	Gamma Glutamyl Transferase	0.35

Output Group	Output	Correlation
Labs & Vitals	Glucose	0.34
Labs & Vitals	Heart Rate	0.48
Labs & Vitals	Hematocrit	0.41
Labs & Vitals	Hemoglobin	0.42
Labs & Vitals	Hemoglobin A1c	0.47
Labs & Vitals	Lactate Dehydrogenase	0.66
Labs & Vitals	Lymphocytes	0.40
Labs & Vitals	Monocytes	0.56
Labs & Vitals	Neutrophils	0.42
Labs & Vitals	Phosphorus	0.54
Labs & Vitals	Plasma Neurofilament Light (NfL)	0.47
Labs & Vitals	Platelet	0.32
Labs & Vitals	Potassium	0.55
Labs & Vitals	Protein	0.45
Labs & Vitals	Respiratory Rate	0.52
Labs & Vitals	Sodium	0.51
Labs & Vitals	Systolic Blood Pressure	0.52
Labs & Vitals	Temperature	0.53
Labs & Vitals	Total Bilirubin	0.39

Output Group	Output	Correlation
Labs & Vitals	Triglycerides	0.44
Labs & Vitals	Uric Acid	0.32
Labs & Vitals	Weight	0.33

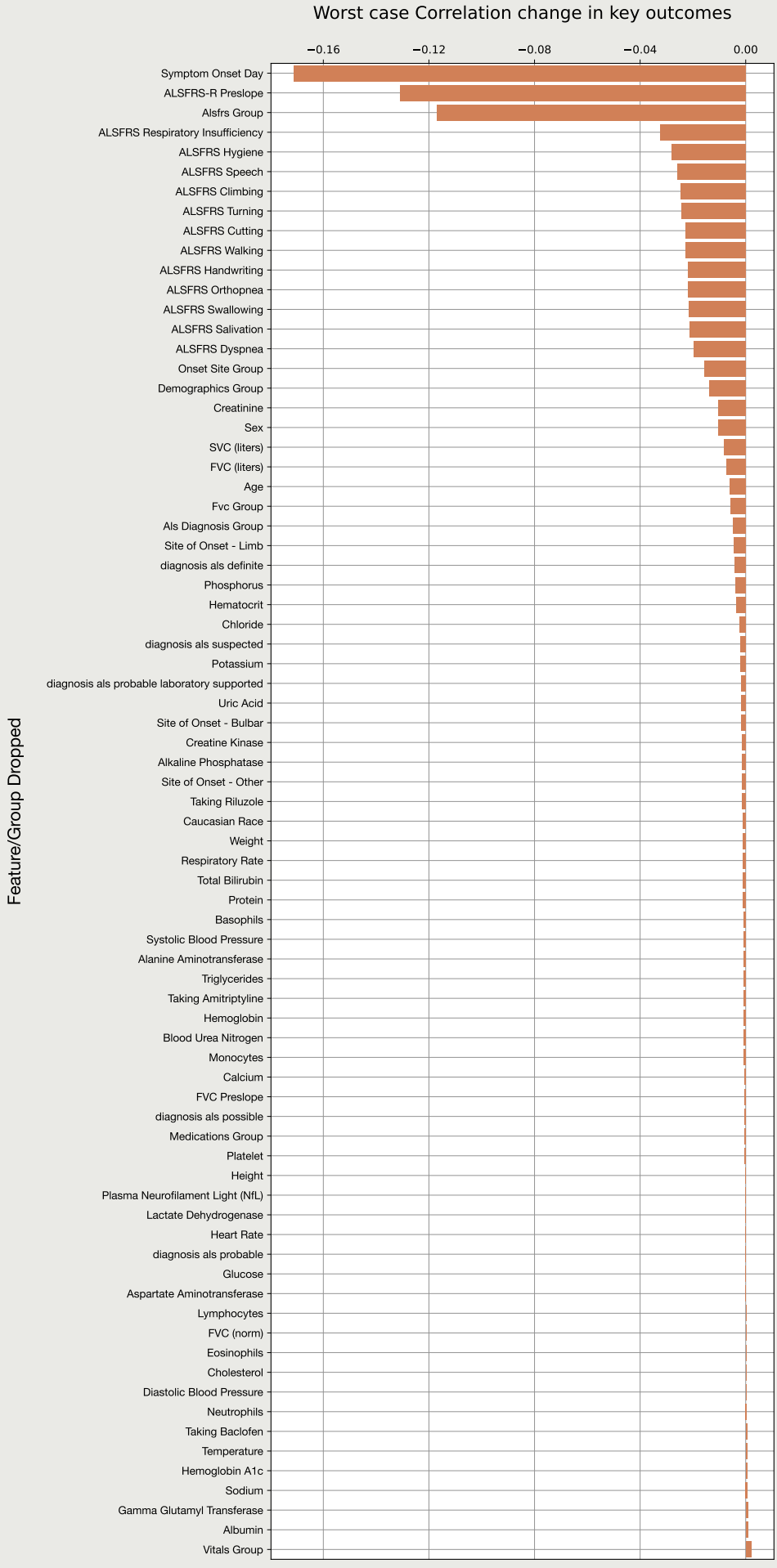
The full population captured in the dataset includes participants with a variety of diagnoses. The following table presents the correlation performance of the DTG on these various cohorts.

Output	**Correlation** Full Population	**Correlation** Recent Onset of Symptoms	**Correlation** Minimum Vital Capacity
ALSFRS-R Score	0.43	0.35	0.40
FVC	0.41	0.41	0.43

DTG Performance Sensitivity

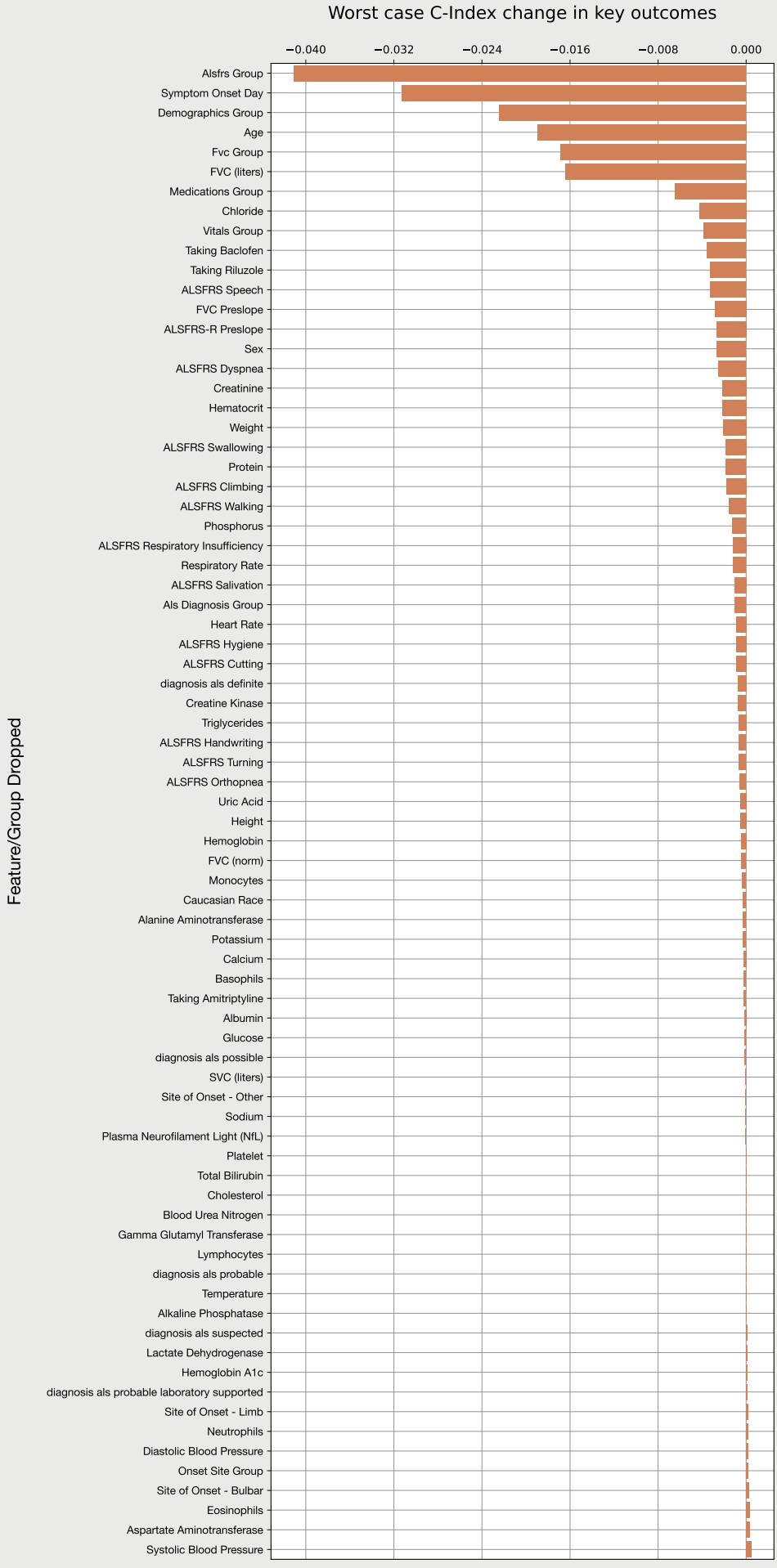
Previous sections on DTG performance assume that all DTG Input Requirements are present at baseline. This section investigates the sensitivity to missing inputs by removing either single inputs or common groups of inputs for all participants at baseline. The resulting worst case change in correlation for other key outcomes is presented. The table highlights changes greater than 0.03 in correlation while the graph presents the full analysis for all inputs.

Feature/group dropped	**Change in Correlation**
Symptom Onset Day	-0.17
ALSFRS-R Preslope	-0.13
Alsfrs Group	-0.12
ALSFRS Respiratory Insufficiency	-0.03


Worst case Correlation change in key outcomes
−0.16
−0.12
−0.08
−0.04
0.00
Feature/Group Dropped
Symptom Onset Day
ALSFRS-R Preslope
Alsfrs Group
ALSFRS Respiratory Insufficiency
ALSFRS Hygiene
ALSFRS Speech
ALSFRS Climbing
ALSFRS Turning
ALSFRS Cutting
ALSFRS Walking
ALSFRS Handwriting
ALSFRS Orthopnea
ALSFRS Swallowing
ALSFRS Salivation
ALSFRS Dyspnea
Onset Site Group
Demographics Group
Creatinine
Sex
SVC (liters)
FVC (liters)
Age
Fvc Group
Als Diagnosis Group
Site of Onset - Limb
diagnosis als definite
Phosphorus
Hematocrit
Chloride
diagnosis als suspected
Potassium
diagnosis als probable laboratory supported
Uric Acid
Site of Onset - Bulbar
Creatine Kinase
Alkaline Phosphatase
Site of Onset - Other
Taking Riluzole
Caucasian Race
Weight
Respiratory Rate
Total Bilirubin
Protein
Basophils
Systolic Blood Pressure
Alanine Aminotransferase
Triglycerides
Taking Amitriptyline
Hemoglobin
Blood Urea Nitrogen
Monocytes
Calcium
FVC Preslope
diagnosis als possible
Medications Group
Platelet
Height
Plasma Neurofilament Light (NfL)
Lactate Dehydrogenase
Heart Rate
diagnosis als probable
Glucose
Aspartate Aminotransferase
Lymphocytes
FVC (norm)
Eosinophils
Cholesterol
Diastolic Blood Pressure
Neutrophils
Taking Baclofen
Temperature
Hemoglobin A1c
Sodium
Gamma Glutamyl Transferase
Albumin
Vitals Group

This table highlights changes greater than 0.03 in c-index for death events while the graph presents the full analysis for all inputs.

Feature/group dropped	Change in C-Index
Alsfrs Group	-0.04
Symptom Onset Day	-0.03


Worst case C-Index change in key outcomes
−0.040
−0.032
−0.024
−0.016
−0.008
0.000
Feature/Group Dropped
Alsfrs Group
Symptom Onset Day
Demographics Group
Age
Fvc Group
FVC (liters)
Medications Group
Chloride
Vitals Group
Taking Baclofen
Taking Riluzole
ALSFRS Speech
FVC Preslope
ALSFRS-R Preslope
Sex
ALSFRS Dyspnea
Creatinine
Hematocrit
Weight
ALSFRS Swallowing
Protein
ALSFRS Climbing
ALSFRS Walking
Phosphorus
ALSFRS Respiratory Insufficiency
Respiratory Rate
ALSFRS Salivation
Als Diagnosis Group
Heart Rate
ALSFRS Hygiene
ALSFRS Cutting
diagnosis als definite
Creatine Kinase
Triglycerides
ALSFRS Handwriting
ALSFRS Turning
ALSFRS Orthopnea
Uric Acid
Height
Hemoglobin
FVC (norm)
Monocytes
Caucasian Race
Alanine Aminotransferase
Potassium
Calcium
Basophils
Taking Amitriptyline
Albumin
Glucose
diagnosis als possible
SVC (liters)
Site of Onset - Other
Sodium
Plasma Neurofilament Light (NfL)
Platelet
Total Bilirubin
Cholesterol
Blood Urea Nitrogen
Gamma Glutamyl Transferase
Lymphocytes
diagnosis als probable
Temperature
Alkaline Phosphatase
diagnosis als suspected
Lactate Dehydrogenase
Hemoglobin A1c
diagnosis als probable laboratory supported
Site of Onset - Limb
Neutrophils
Diastolic Blood Pressure
Onset Site Group
Site of Onset - Bulbar
Eosinophils
Aspartate Aminotransferase
Systolic Blood Pressure

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- A subset of the data used in preparation of this document were obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database. The data available in the PRO-ACT Database have been volunteered by PRO-ACT Consortium members.
- A subset of the data used in preparation of this document were obtained from NEALS. We acknowledge the NEALS Biorepository for providing all or part of the biofluids from the ALS, healthy controls and non-ALS neurological controls used in this study.
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- A subset of the data used in preparation of this document were obtained from ANSWER ALS Data Portal (AALS-01184). Up-to-date information on the study.
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- A subset of the data used in preparation of this document were obtained form the Pooled Resource Open-Access Clinical Research (PRO-ACE) Database. The data available in the PRO-ACE Database have been volunteered by PRO-ACE Consortium members.

Release Notes

- Updated model architecture.
- Improved generalization performance.

Additional Resources

- New DTG architecture
- Creating digital twins with Neural Boltzmann Machine
- Personalized p-values with DTGs

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