Prediction of individual progression rate in Parkinson's disease using clinical measures and biomechanical measures of gait and postural stability

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45th International Conference on Acoustics, Speech, and Signal Processing
May 8, 2020

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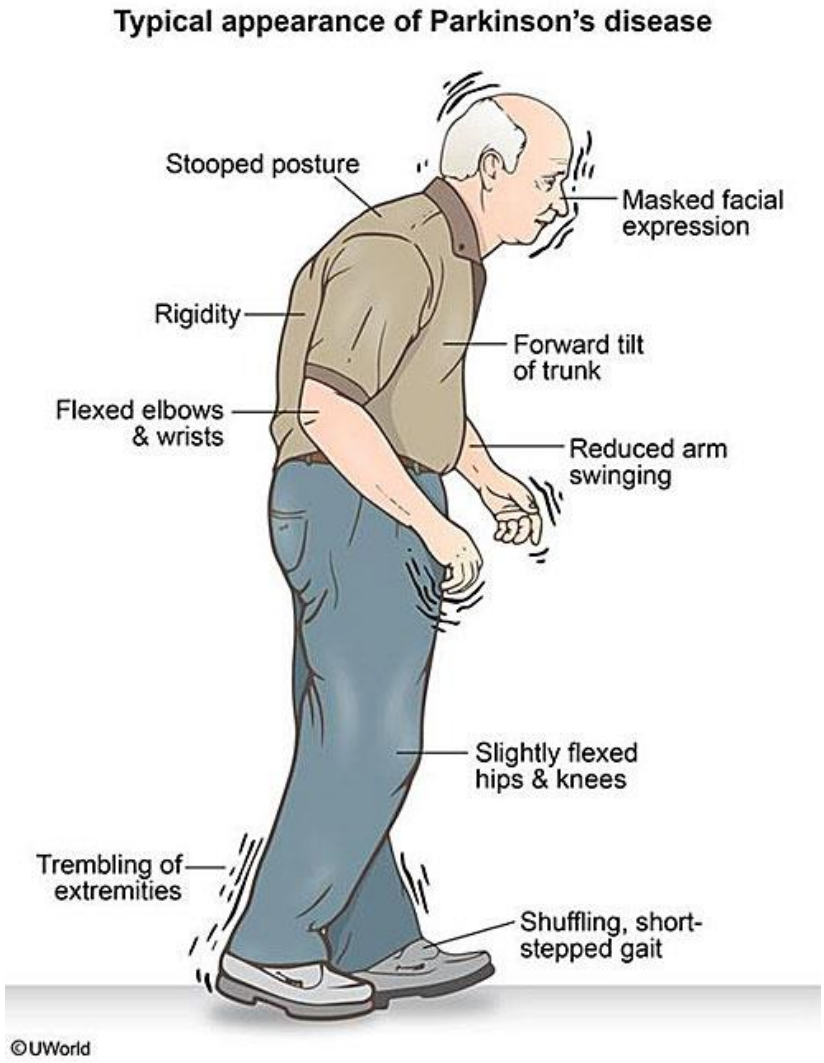
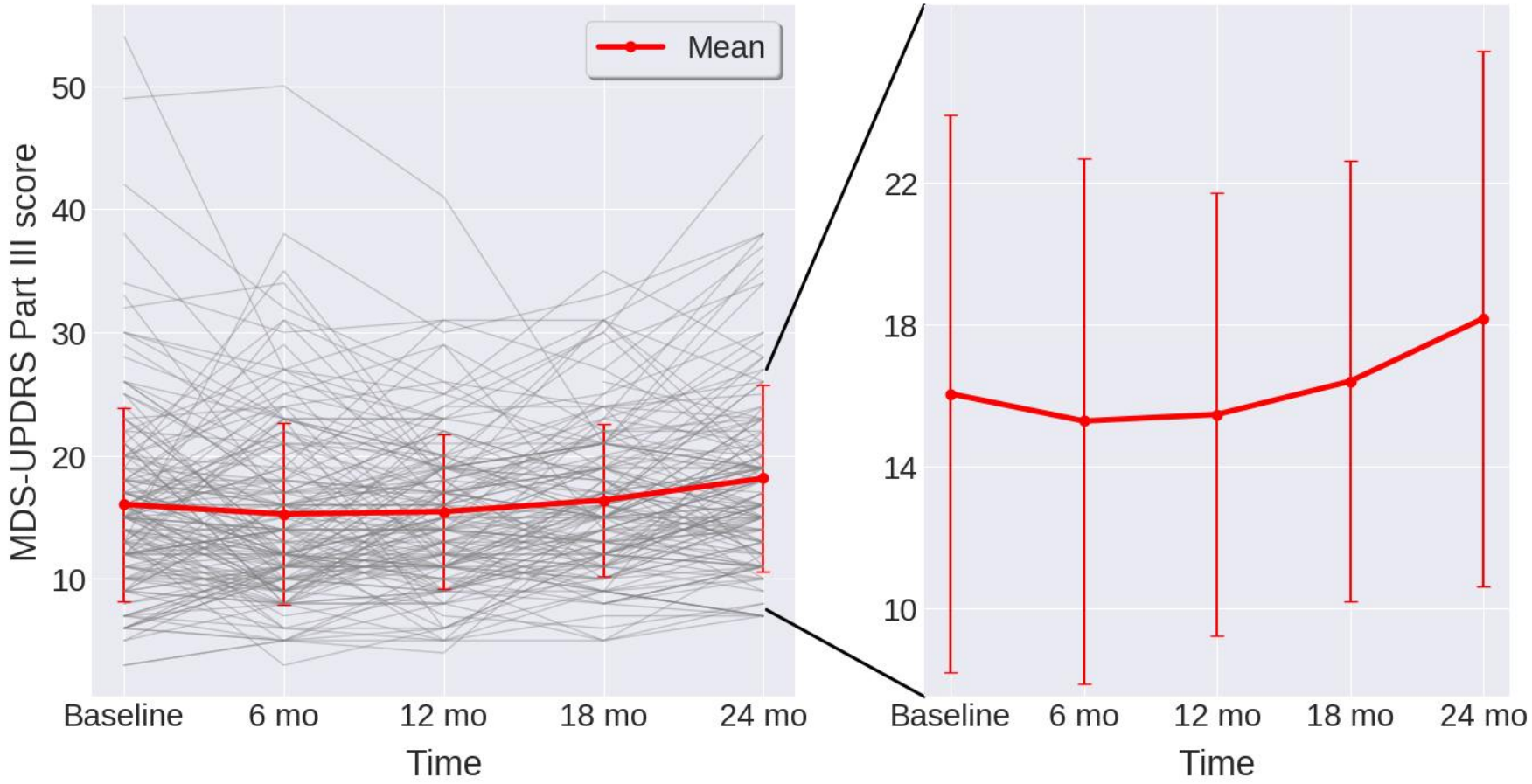
Background: Parkinson's Disease

- **Parkinson's Disease (PD) is a devastating neurodegenerative disease characterized by resting tremor, limb stiffness, and bradykinesia**
  - **Second most common neurodegenerative disorder**
  - **Current treatments (such as dopaminergic drugs) alleviate symptoms are *not* cures**



Background: Problem

- **There is no clinically accepted method to predict individual progression rate.**



Goal of this work

- **A model that can predict individual progression rate and accurately identify fast progressors.**

- **This would allow:**
  - **Informing patient decision making and patient management**
  - **Expedite the identification of a disease modifying therapy**
    - **Drug trials are expensive**
      - **Average total cost of developing a new drug is between $2 to $3 billion[1].**

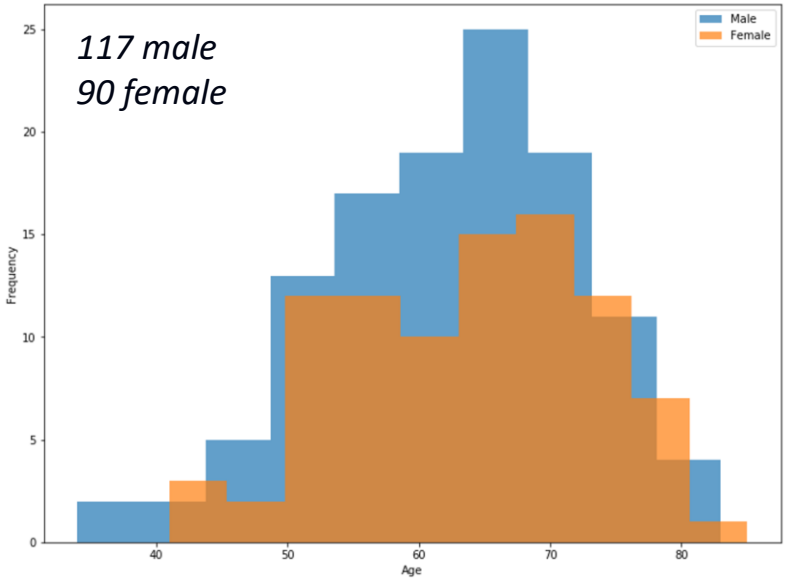
    - **Identifying fast progressors can enrich trial selection and enabling accurate identification of effective disease modifying candidate drugs within the duration of a clinical trial (typically 2 years)**

1. https://www.jhsph.edu/news/news-releases/2018/cost-of-clinical-trials-for-new-drug-FDA-approval-are-fraction-of-total-tab.html

Data: Subjects

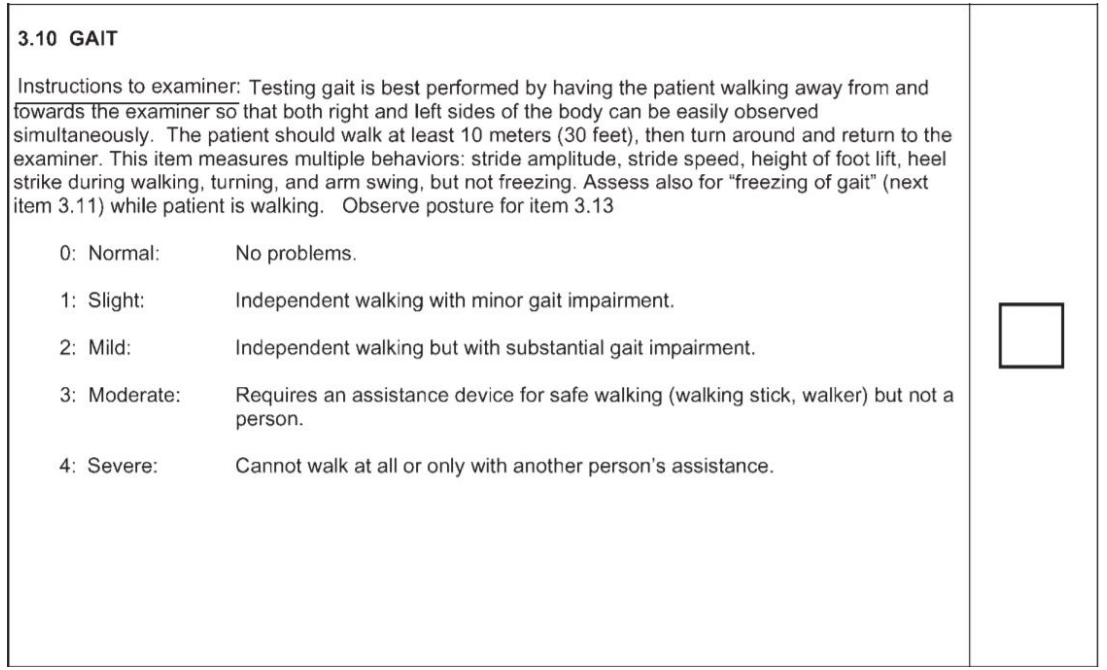
- **160 PD subjects from the NIH-NINDS funded Parkinson's Disease Biomarkers Program (PDBP)**
  - **Followed longitudinally for 2 years at UTSW by Dr. Richard B. Dewey Jr.**
  - **Disease severity measured by the Movement Disorder Society revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)**

Age histogram



Data: Prediction target

- MDS-UPDRS is a four-part assessment of PD severity conducted by a trained examiner
- Part III: Motor Examination
  - 18 sections
  - e.g.- Speech, facial expression, gait
  - Scale of 0 (normal) to 4 (severe)
- Conducted when patients on-medication
- To eliminate rater as a confound, one rater was used throughout the study



3.10 GAIT

Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for "freezing of gait" (next item 3.11) while patient is walking. Observe posture for item 3.13

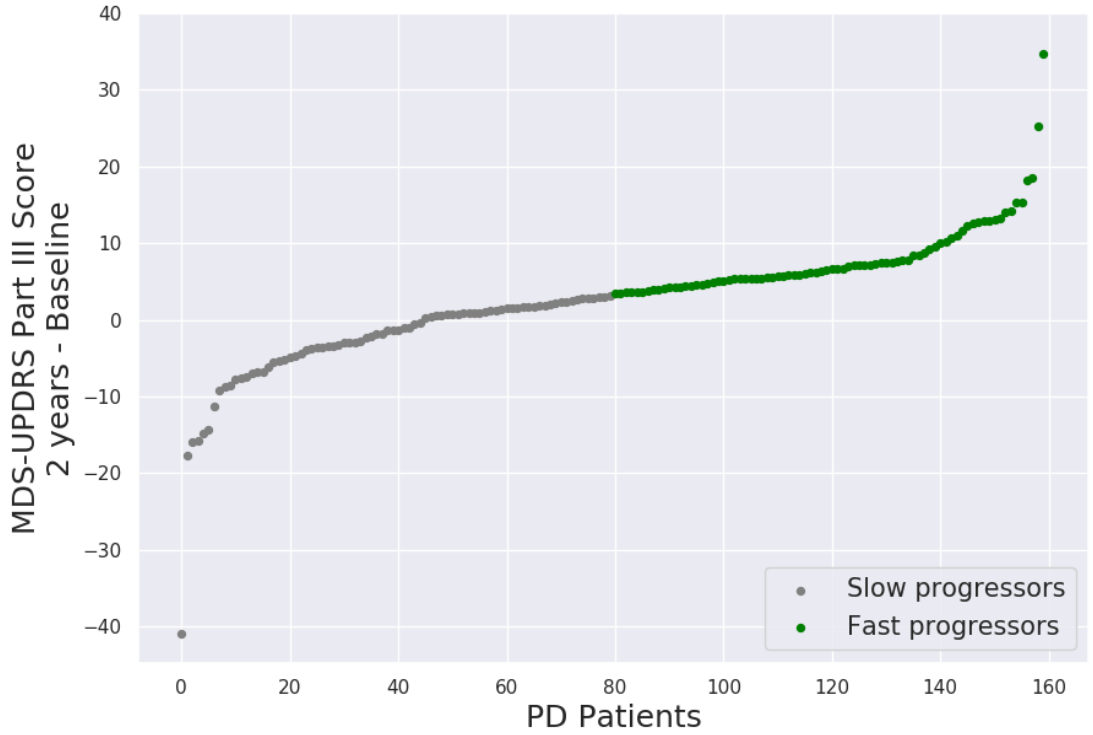
0:	Normal:	No problems.
1:	Slight:	Independent walking with minor gait impairment.
2:	Mild:	Independent walking but with substantial gait impairment.
3:	Moderate:	Requires an assistance device for safe walking (walking stick, walker) but not a person.
4:	Severe:	Cannot walk at all or only with another person's assistance.

Goetz, Christopher G., et al. (2008). "Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results."

Data: Prediction target

3 targets are predicted in this research:

1. $2\ years$ **MDS-UPDRS Part III**
2. $2\ years\ -Baseline$ **MDS-UPDRS Part III**
3. $\frac{2\ years\ -Baseline}{Baseline}$ **MDS-UPDRS Part III**



Data: Features

- **Previous literature has found gait and postural stability characteristics to be associated with current risk[1], progression[2], and diagnosis[3]**

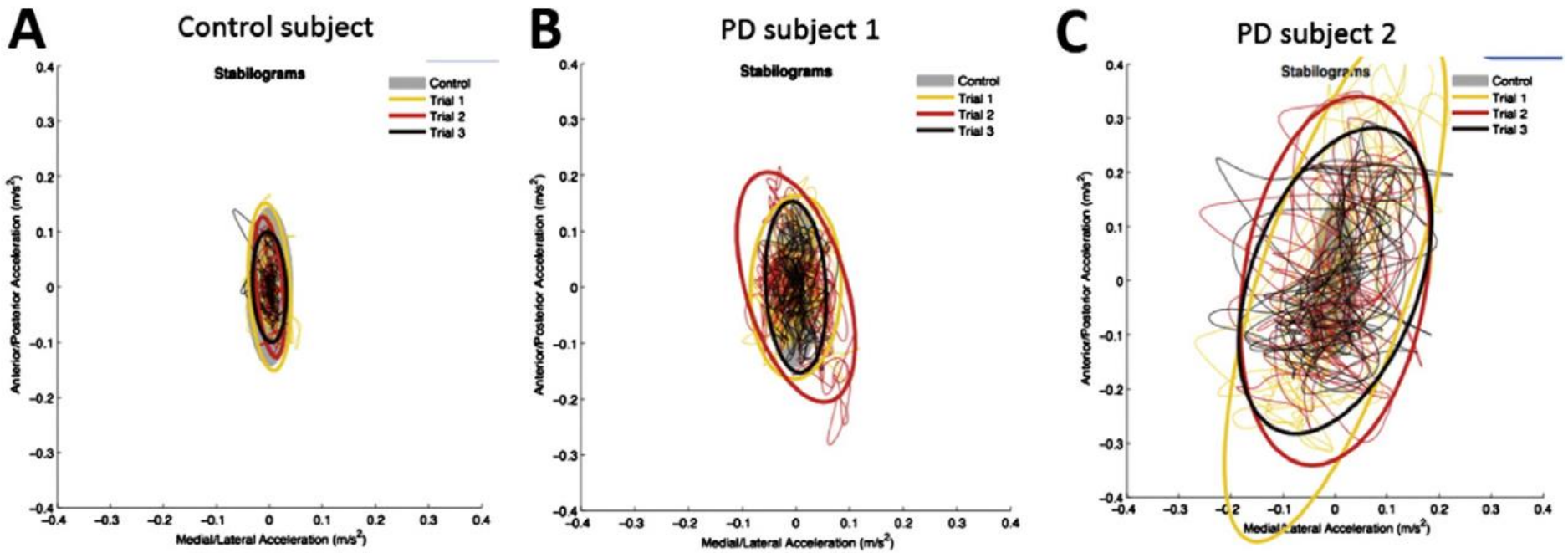


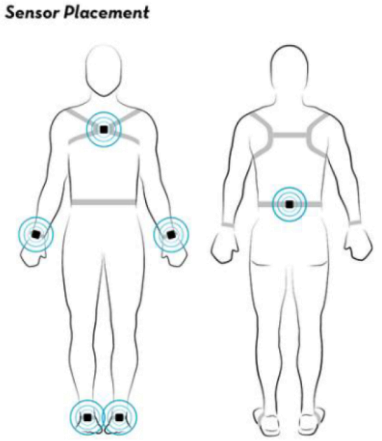
Fig. 2. Plots of the sway path in anteroposterior and mediolateral directions in a control subject (A) and two PD subjects with clinically normal balance (B, C).

Dewey, D. Campbell, et al. (2014) "Automated gait and balance parameters diagnose and correlate with severity in Parkinson disease."

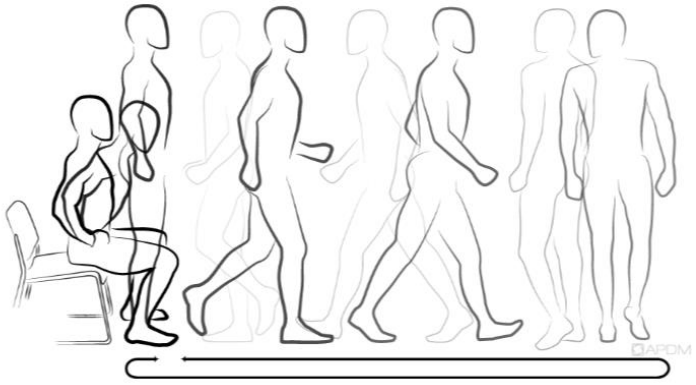
1. Rovini, E. et al. (2017) How wearable sensors can support parkinson's disease diagnosis and treatment: A systematic review.
2. Galna, B et al. (2015) Progression of Gait Dysfunction in Incident Parkinson's Disease: Impact of Medication and Phenotype.
3. Jankovic, J. (2008) Parkinson's disease: Clinical features and diagnosis.

Data: Features

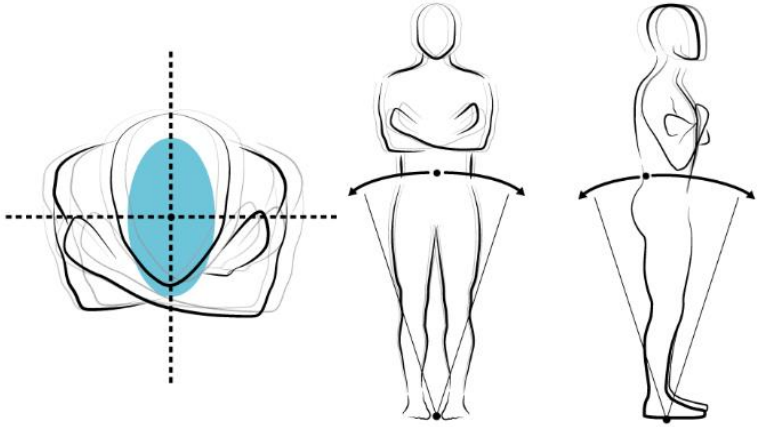
- **Biomechanical gait and postural stability measures**
  - Six movement sensors (accelerometer, gyroscope, and magnetometer)
  - APDM Mobility Lab using Opals® sensors
  - Conducted when patient is on-medication
  - 2 mobility tasks:



- instrumented Timed-Up-and-Go (iTUG) test
  - Subjects stand up, walk 6m, turn 180° walk back to chair and sit down.



- instrumented Sway (iSway) test
  - Subjects stand still with hands across their chests and feet positioned a set distance apart

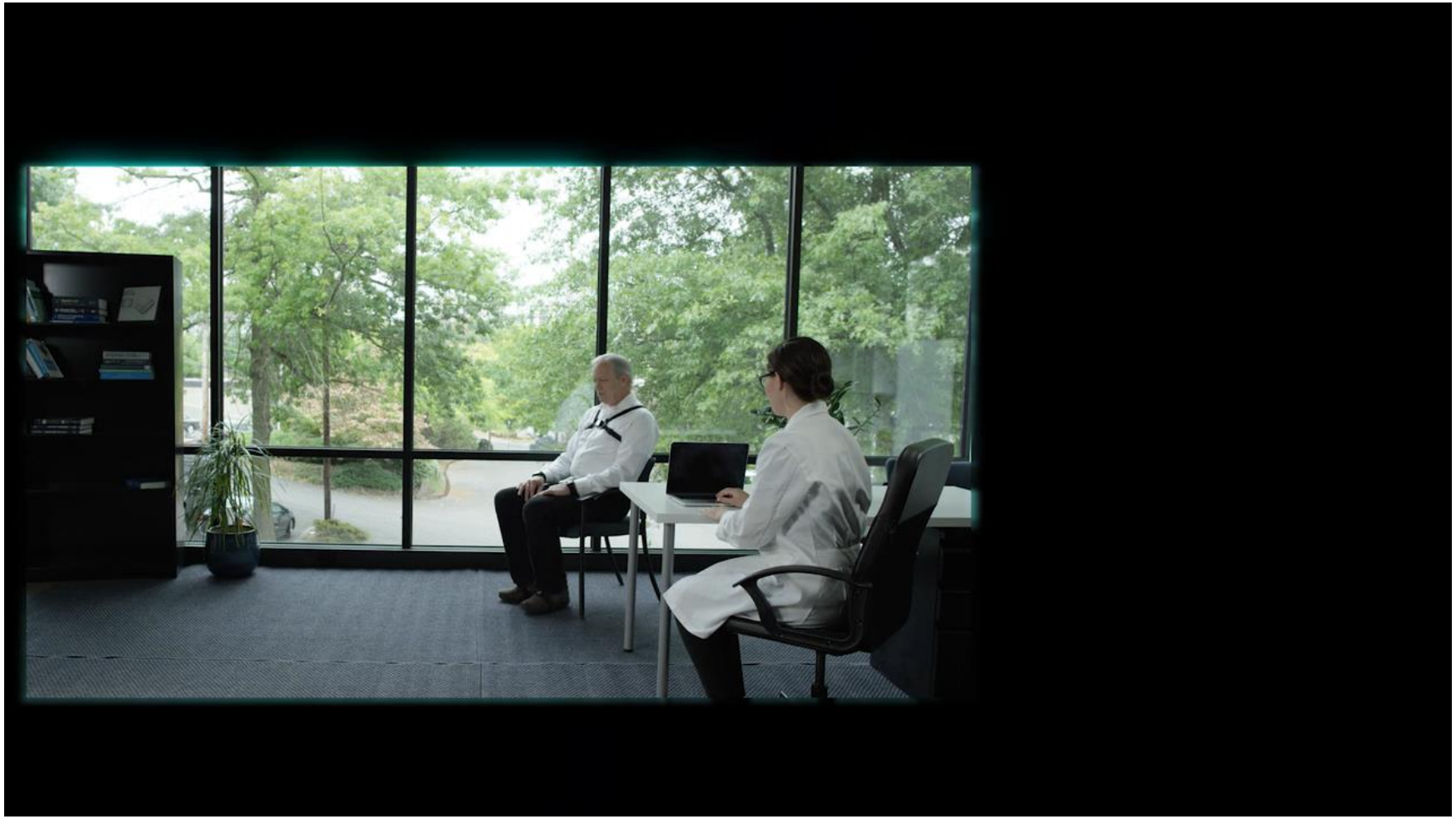


https://www.apdm.com/mobility/

Data: Features

- **iTUG video:**

https://www.apdm.com/mobility/



Data: Features

- **Clinical and demographic features**
  - **Age**
  - **Gender**
  - **Baseline MDS-UPDRS Part III scores**
  - **Levodopa Equivalent Daily Dose (LEDD)**
  - **Montreal Cognitive Assessment (MOCA) score**

Methods: Feature Set combinations

Feature Set
Baseline iTUG & iSway (148)
6mo-Baseline iTUG & iSway (148)
Asymmetric Baseline iTUG & iSway (22)
Asymmetric 6mo-Baseline iTUG & iSway (22)
Clinical measures (40)

$$1 - \frac{Left\ measure}{Right\ measure}$$

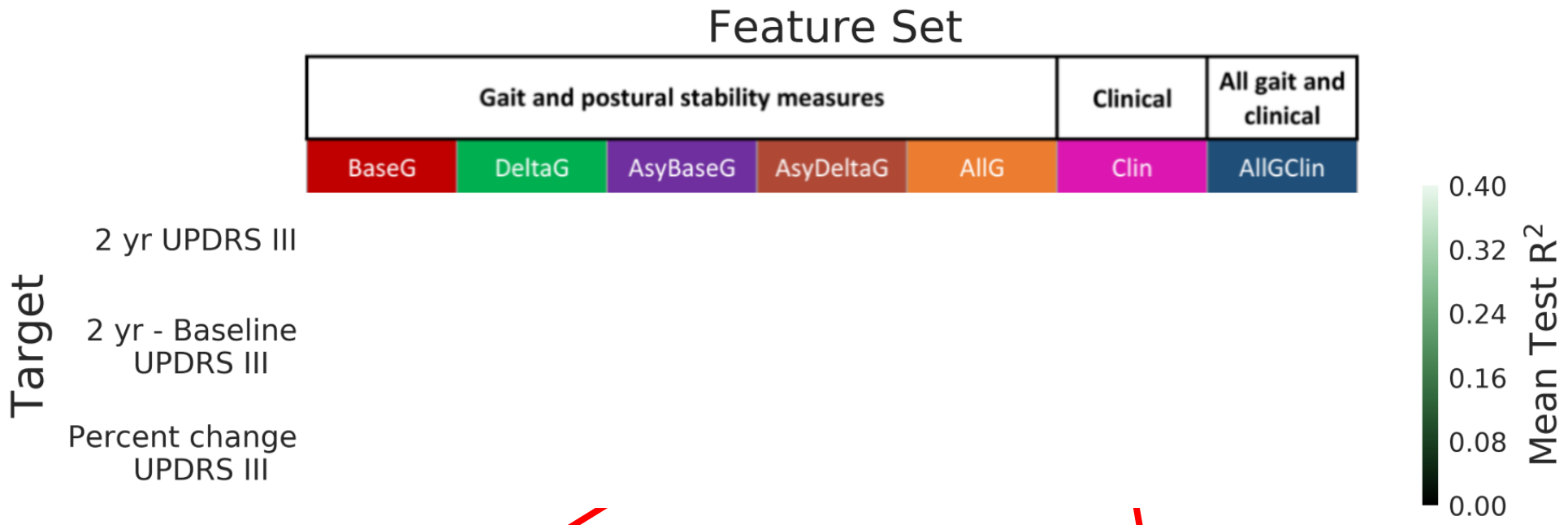
Methods: Partitioning, Modeling, and Feature Importance

- **Partitioning**:
  - Nested K-fold cross validation with 3 inner and 3 outer folds

- **Optimization**:
  - XGBoost and Feed Forward Neural Network (NNs) models used
  - Hyperparameter optimization and model selection on inner folds using random search
  - Random search of hyperparameter space ensures unbiased model tuning largely independent of ML experience
  - Performance evaluated using R^2 score on held-out partitions

- **Feature Importance**:
  - Feature permutation importance analysis
  - Each feature randomly permuted 100 times and decrease in performance measured

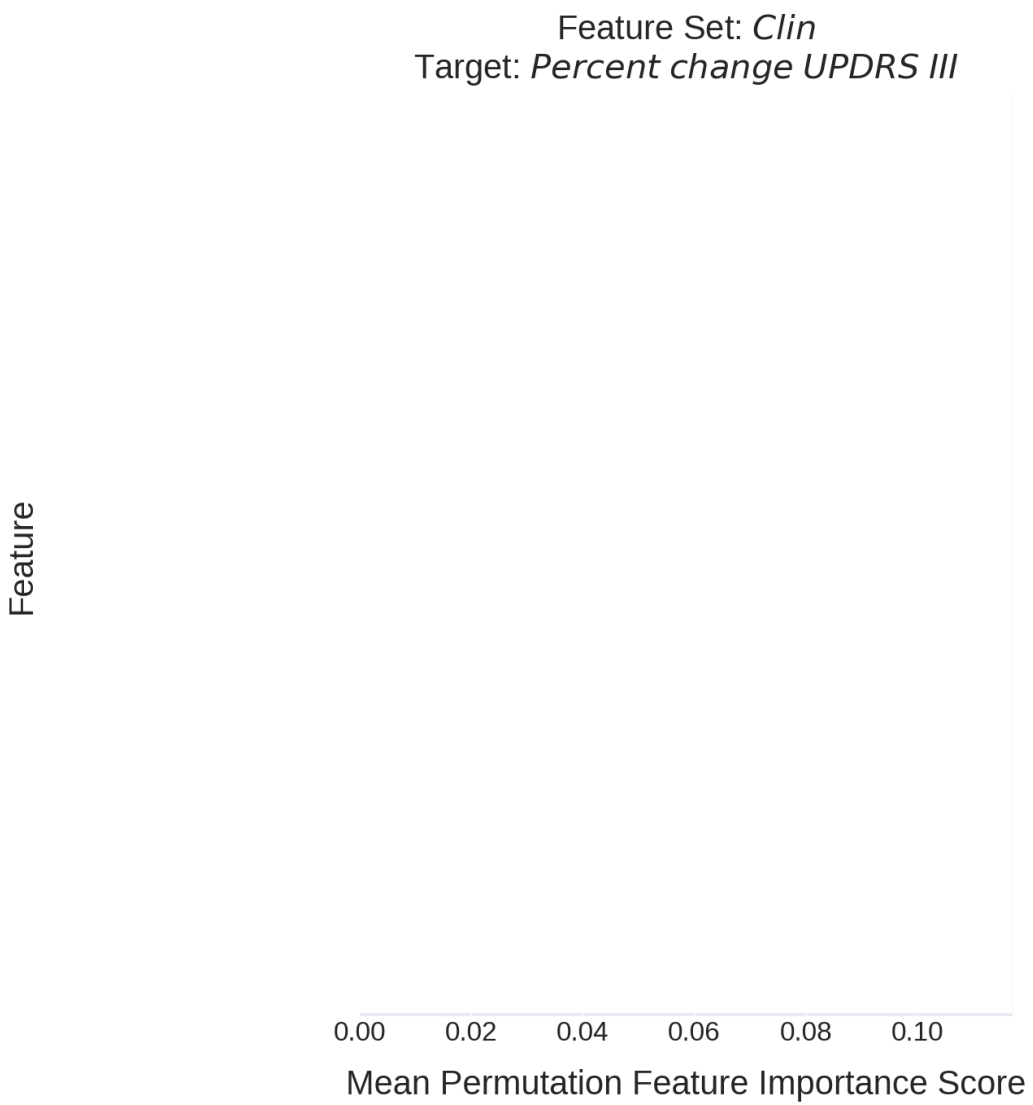
Results on test set : Clinical measures have most predictive power



- **Biomechanical measures alone were also able to explain a substantial 21% of variance.**
- **First study to show biomechanical measures have prognostic value for future severity.**

- **Comparable to 41% performance achieved by Latourelle et al. (2017) on *validation* set**
- **Our model also achieved a PPV of 71% in identifying fast progressors**

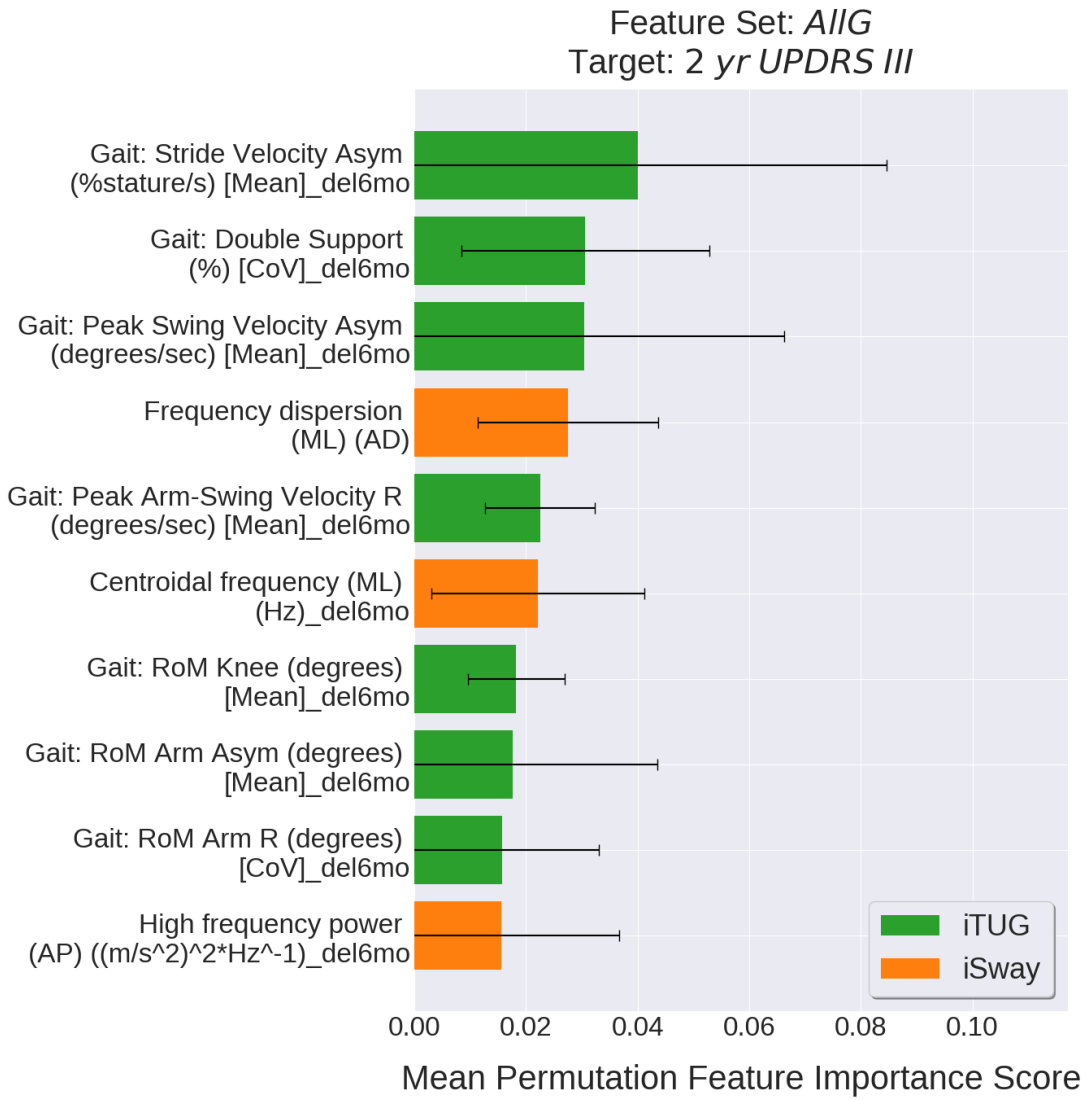
Results: Baseline MDS-UPDRS III scores most important



- **Important clinical measures:**
  - **Upper extremity, hand, neck, and total MDS-UPDRS III scores rank highest in feature importance**

Results: 6mo-Baseline gait features also important

- **Important biomechanical measures**:
  - **6mo-Baseline Gait measures rank highest**



Strengths, Limitations and Future work

- **Strengths**
  - This is a comparatively large (160 subjects) study performed with rigorous *nested* cross-validation.

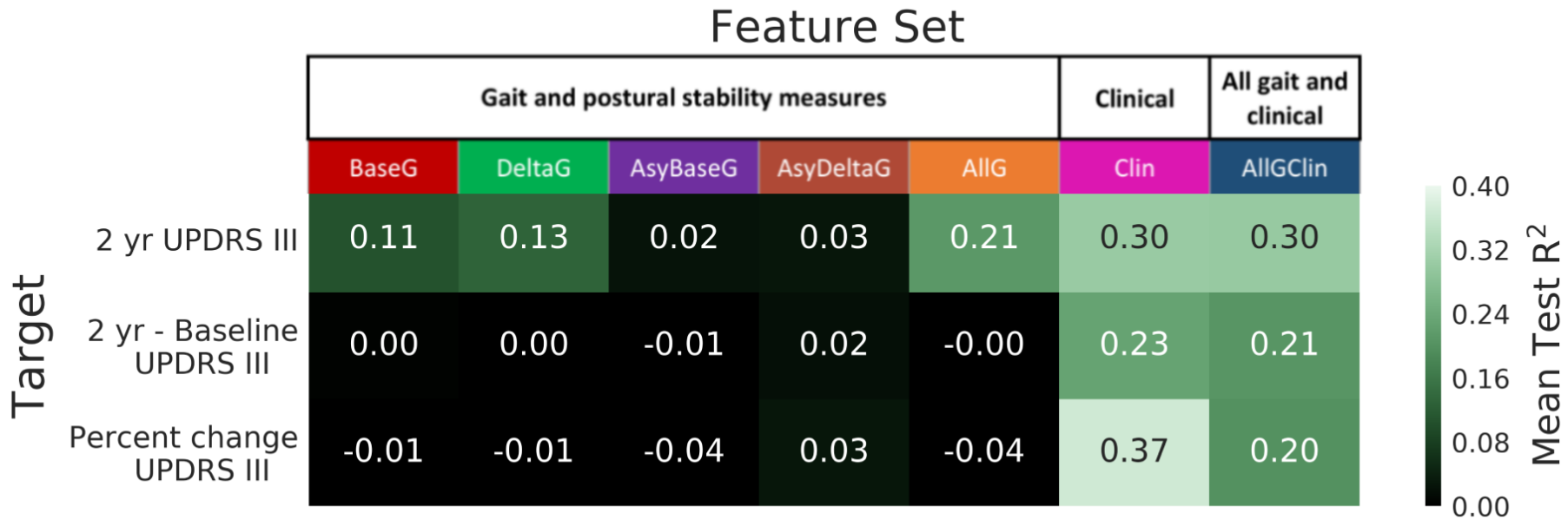
- **Limitations: Single dataset**:
  - Replication on independent dataset would further confirm findings

- **Future work: learn to construct biomechanical features from raw sensor data**:
  - iTUG and iSway measures were constructed from the sensor data using the APDM Mobility Lab software
  - These pre-engineered features may lose some information that could be used by the predictive models
  - Future studies on analyzing the raw sensor data may further boost predictive power

Conclusions

- **Potential to enrich clinical trials:**
  - **Our best predictive model achieves a 71% PPV in identifying fast progressors on held out test data not used in training or validation.**
  - **This can be used to expedite clinical trials to more rapidly identify a disease modifying drug**

- **Predictive power of biomechanical measures:**
  - **This is the first study to show the predictive power of biomechanical measures using machine learning**



Acknowledgements

Deep Learning for Precision Health lab www.utsoutwestern.edu/labs/montillo

Prof Albert Montillo 

Dr. Son Nguyen 

Cooper Mellema 

Kevin Nguyen 

Alex Treacher 

Krishna Chitta 

Dr. Zhiguo Shang 

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Dr. Richard B. Dewey Jr. 

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Funding:

NIH U01NS082148
NIH R01-AG059288
NIH U01 CA207091-01A1
NIH F31-NS115348
Lyda Hill Foundation
Green Fellowship
UTSW SURF

UT Southwestern
Lyda Hill Department of Bioinformatics

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