

# A digital measure for Huntington's Disease

HDDMS: a score for the sensitive assessment of disease progression

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# Huntington's disease

- **Prevalence 1 ~ 10,000**
- Genetic disease (50% chance to inherit from parent) described as **ALS, Parkinson's disease and Alzheimer's disease rolled into one**
- **Usually strikes in the prime of life;** first symptoms typically appear between **age of 30–50 years, although may occur earlier or later.**
- Triad of symptoms that include **cognitive, behavioural and motor dysfunction**
- Affects families across generations and leads to early loss of ability to work, **may lead to cross-generational poverty**
- **No treatment exists to slow or stop disease progression,** but multiple therapies in development
- **Limited sensitivity of clinical assessments** leads to large and lengthy clinical trials

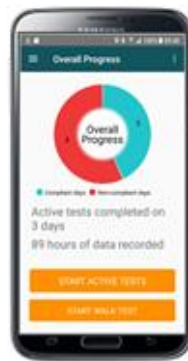


Picture credit: S. Murray and CT Murray 2001. The Lancet 358(S38)

# HD digital biomarker suite - Active tasks and passive monitoring

| ACTIVE TESTS |          |                 |              |                        |                  |                  |                    |                  |        |
|--------------|----------|-----------------|--------------|------------------------|------------------|------------------|--------------------|------------------|--------|
| PROs*        |          | Cognitive tests |              | Upper body motor tests |                  |                  | Stability and gait |                  |        |
| Daily Qs     | EQ-5D-5L | SDMT            | Word reading | Speeded tapping        | Draw a shape     | Chorea           | Balance            | U-Turn           | Walk   |
|              |          |                 |              |                        |                  |                  |                    |                  |        |
| Daily        | Weekly   | Monthly         | Monthly      | Alternating Days       | Alternating Days | Alternating Days | Alternating Days   | Alternating Days | Weekly |

| PASSIVE MONITORING         |              |                 |
|----------------------------|--------------|-----------------|
| Activities of daily living |              |                 |
| Gait                       | Chorea       | Activity levels |
|                            |              |                 |
| Continuously               | Continuously | Continuously    |

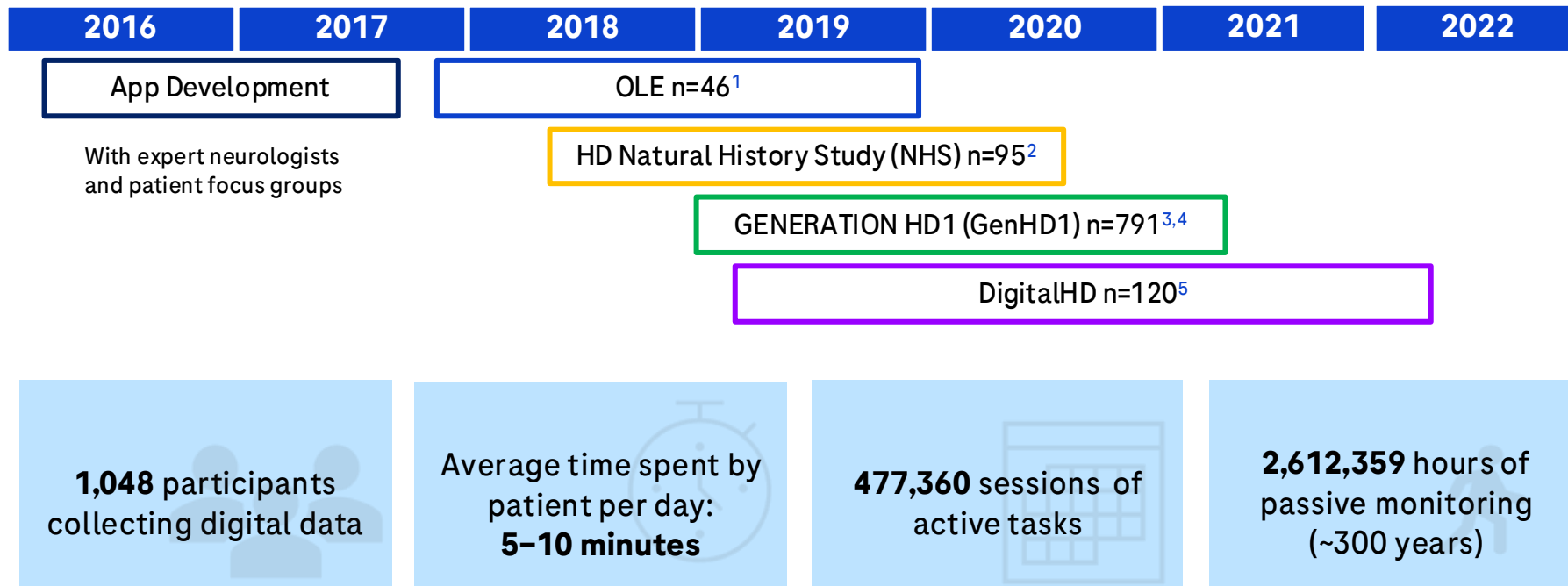


Data is securely transferred to Roche via WiFi for analysis

\* PROs and some assessment schedules differed across GENERATION HD1, HD Natural History, OLE, and Digital HD study

# HD digital biomarker development

Data collected from multiple observational studies and clinical trials



HD, Huntington's disease; OLE, open-label extension; NHS, natural history study.

1. Clinicaltrials.gov/ct2/show/NCT03342053 (Accessed January 2024); 2. Clinicaltrials.gov/ct2/show/NCT03664804 (Accessed January 2024); 3. Clinicaltrials.gov/ct2/show/NCT03761849 (Accessed January 2024);

4. Roche Press Release. Available at: <https://www.roche.com/media/releases/med-cor-2021-03-22b.htm> (Accessed January 2024);

5. Tortelli R, et al. 15<sup>th</sup> Annual CDHL HD Therapeutics Conference

# The Huntington's disease Digital Motor Score

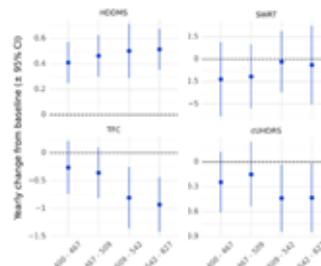
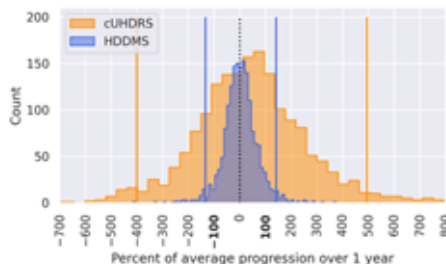
A sensitive assessment of disease progression in Huntington's disease

Sensor-based score

Reduced visit-to-visit variability

Increased sensitivity especially early in disease

Potential to observe clinical signal with 75% smaller sample size



| ISS Stage 2 (DCL 4); 16 months |        |       |       |
|--------------------------------|--------|-------|-------|
|                                | p=0.05 | p=0.1 | p=0.2 |
| cUHDRS                         | 593    | 467   | 341   |
| TFC                            | 695    | 548   | 399   |
| HDDMS                          | 105    | 83    | 60    |

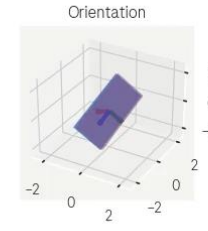
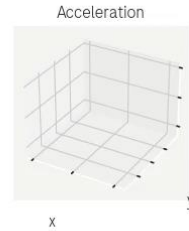
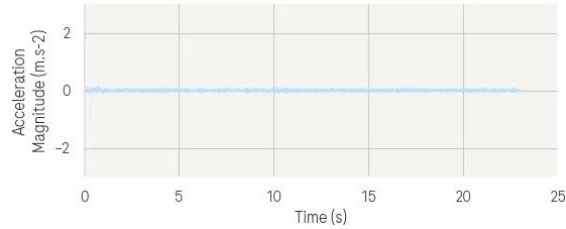
Applied in Huntington's disease drug development at Roche Pharma



Leveraged by other pharmaceutical companies via Roche Diagnostics

# Example: Balance Test

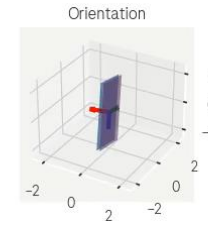
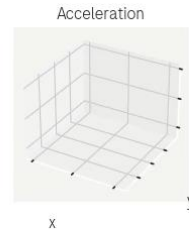
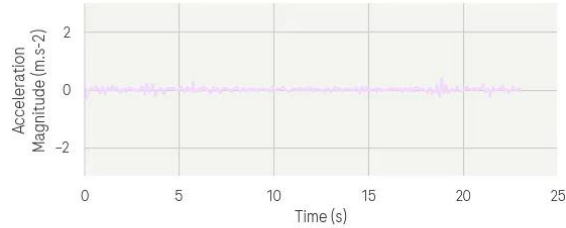
Digital HD study



|             |           |
|-------------|-----------|
| participant | Subject 1 |
|-------------|-----------|

|       |               |
|-------|---------------|
| group | gene negative |
|-------|---------------|

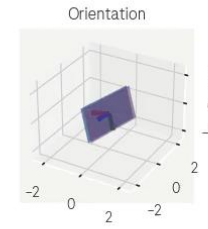
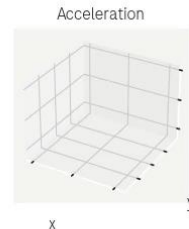
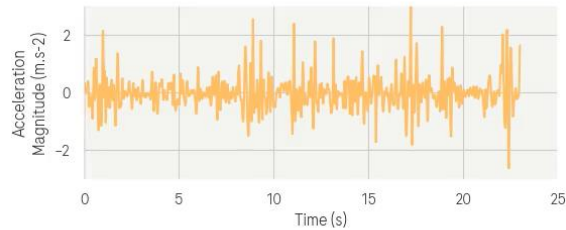
|                       |       |
|-----------------------|-------|
| accelerometer mag std | 0.018 |
|-----------------------|-------|



|             |           |
|-------------|-----------|
| participant | Subject 2 |
|-------------|-----------|

|       |              |
|-------|--------------|
| group | pre-manifest |
|-------|--------------|

|                       |       |
|-----------------------|-------|
| accelerometer mag std | 0.053 |
|-----------------------|-------|



|             |           |
|-------------|-----------|
| participant | Subject 3 |
|-------------|-----------|

|       |          |
|-------|----------|
| group | manifest |
|-------|----------|

|                       |       |
|-----------------------|-------|
| accelerometer mag std | 0.391 |
|-----------------------|-------|

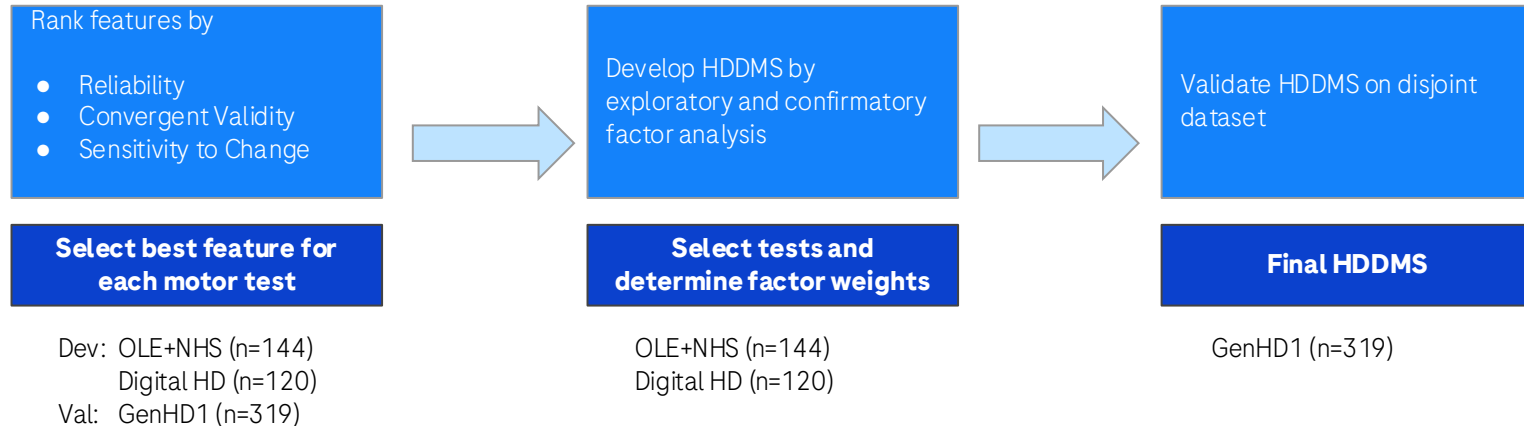
# Developing a digital motor score for Huntington's Disease

Data from separate studies used for development and validation of score based on factor analysis

| Active motor tests                                                                |                                                                                   |                                                                                   |                                                                                     |                                                                                     |                                                                                     |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Balance                                                                           | Chorea                                                                            | Draw a Shape                                                                      | Speeded Tapping                                                                     | Two-Minute Walk                                                                     | U-Turn                                                                              |
|  |  |  |  |  |  |



Extract on average 60 features per test from the raw sensor data

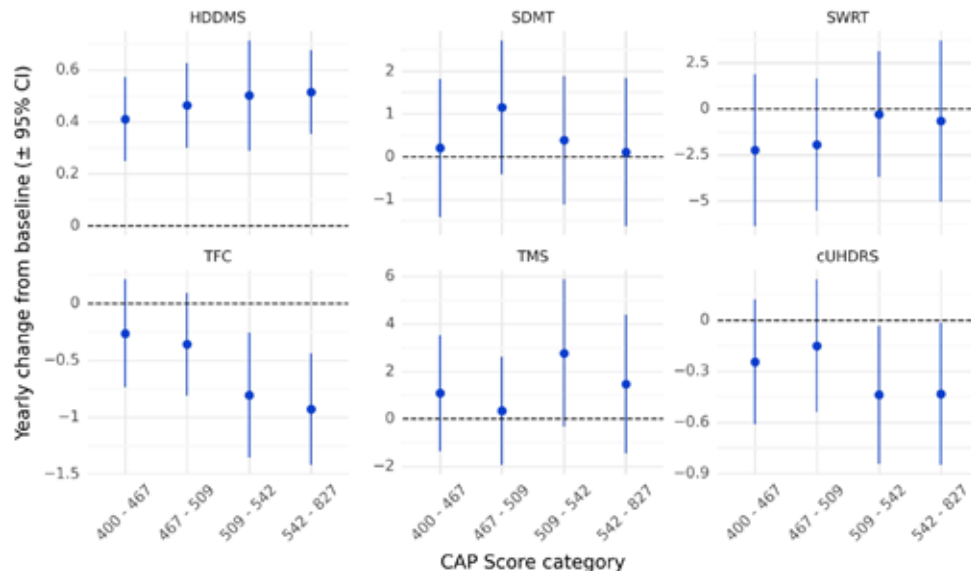
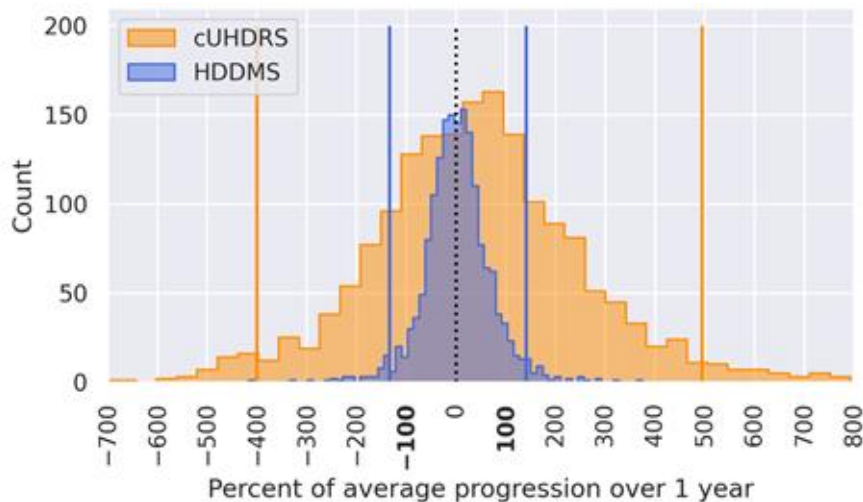


# Reduced variability increases ability to detect progression

Data measured directly from patients on a continuous scale, averaged over multiple days

HDDMS has less visit-to-visit variability than cUHDRS

HDDMS can detect 12-month progression across a range of CAP scores





# The HDDMS has good measurement properties

Significant cross-sectional correlation with clinical anchors (e.g. cUHDRS  $\sim -0.5$ )

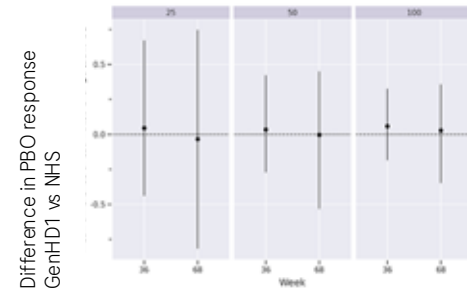
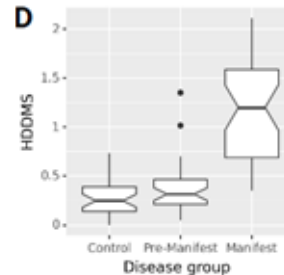
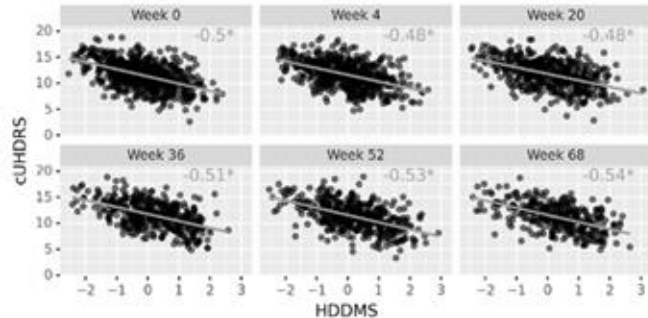
No discernable placebo effect (comparison of GenHD1 PBO arm with NHS)

Good cross-sectional known-groups validity (control vs pre-manifest vs manifest)

High test-retest reliability (ICC $>0.95$  between consecutive fortnights)

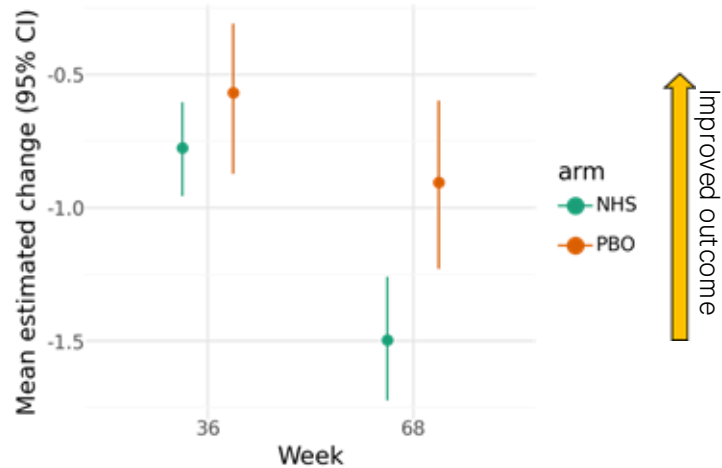
Strong measurement invariance even on test dataset and across timepoints

Significant change-to-change correlation with cUHDRS at 16 months (but not with TFC)

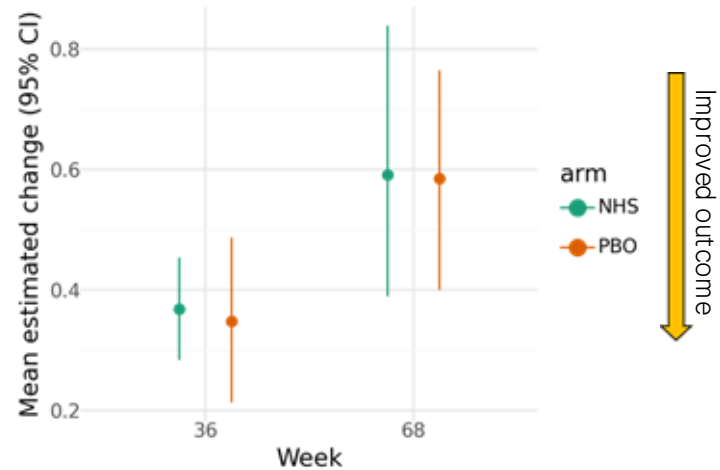


# The HDDMS has limited placebo response

cUHDRS change from baseline



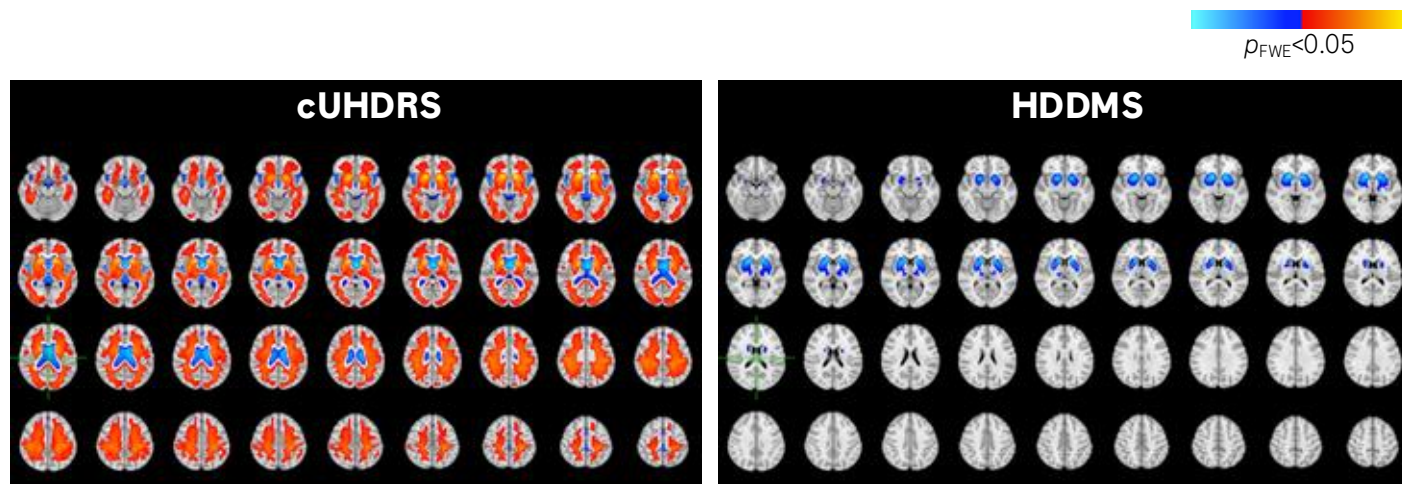
HDDMS change from baseline



# HDDMS may be sensitive to caudate volume shrinkage

Correlation between brain volume and clinical measures of HD

- Shrinkage calculated from deformation gradient used to match MRI scans to template brain
- Colored regions show significant association to clinical measure at baseline: Red - positive association, Blue - negative association

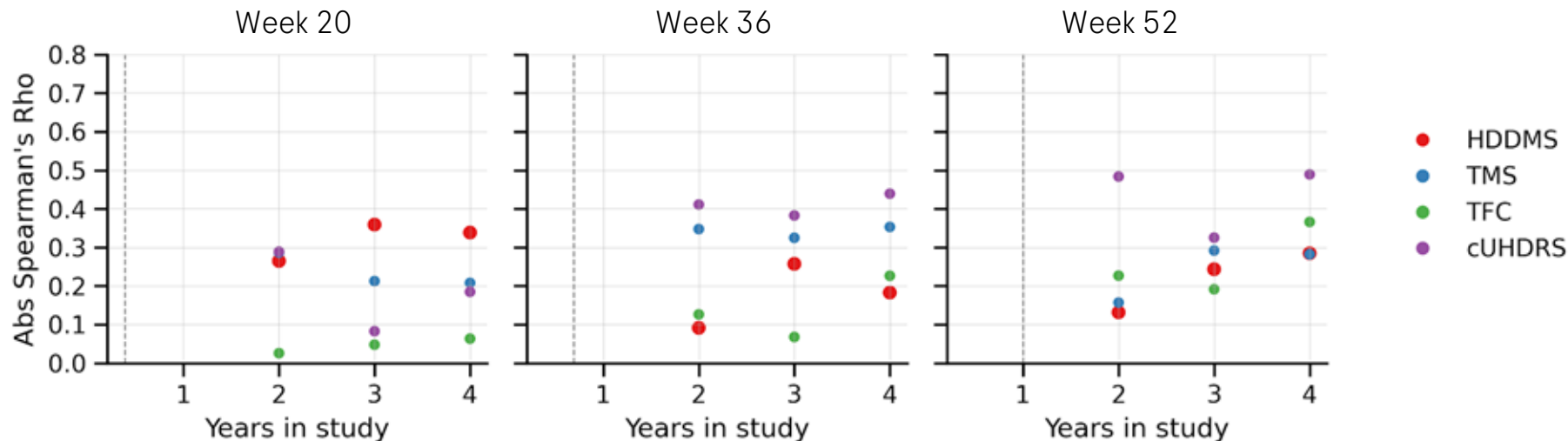


Note that cUHDRS decreases as the disease progresses, whereas HDDMS increases as the disease progresses, so colors appear flipped between cUHDRS and HDDMS  
 cUHDRS, composite unified Huntington's disease rating scale; HD, Huntington's disease; HDDMS, Huntington's disease digital motor score; MRI, magnetic resonance imaging.

# HDDMS prognostic validity

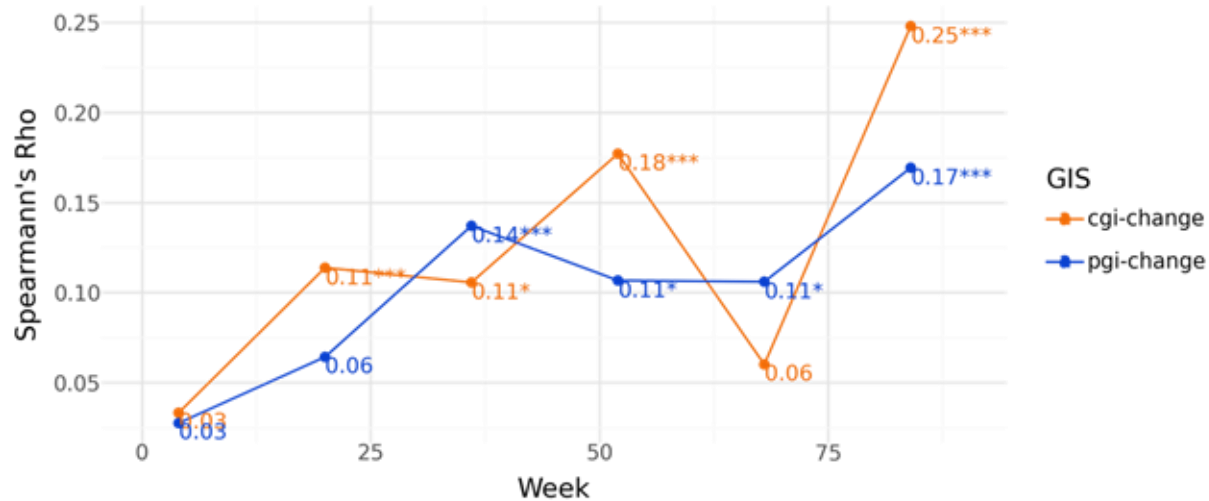
The HDDMS predicts long-term cUHDRS similarly well as the cUHDRS components

Correlation between GENERATION HD1 placebo measure at week X and Enroll-HD cUHDRS progression (n= ~50)



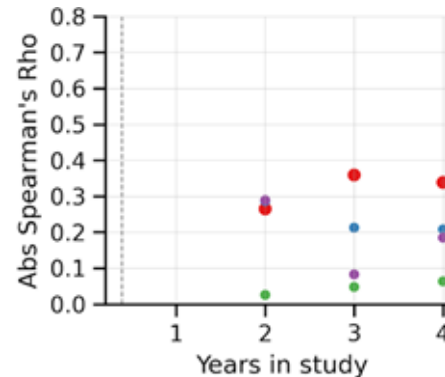
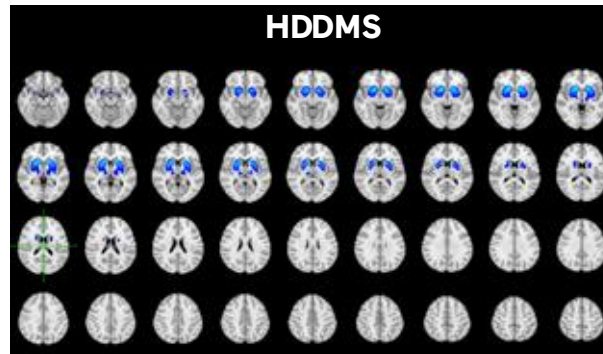
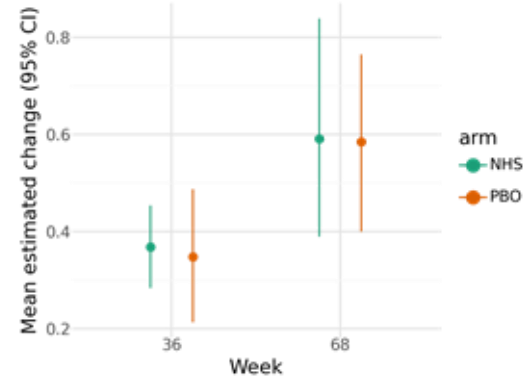
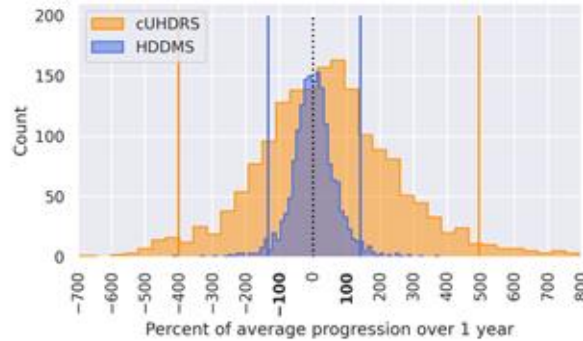
# Change in HDDMS relates to change in CGI/PGI

The longer the observation period, the more strongly the HDDMS relates to global disease progression



# Conclusions

The HDDMS may enable (earlier) decision-making in clinical trials for Huntington's disease



# Acknowledgements

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possible**

**Thank you for your attention**

**Doing now what patients need next**