Newsletter

Jun 23 Issue 30

8 Nations Participating

32 Clinical Sites Worldwide

824 Participants Screened (including longitudinal visits)

Dear HDClarity Teams

REMINDERS

- The **Lab manual has been updated to V6.5** with shipping updated proformas. Please ensure that this version is being used and if a copy is not available, please contact CC.
- Please ensure that all **EDC sampling visit data queries are answered before shipping the associated samples** to Biorep.
- On the day of shipping samples, please remember to **activate the WarmMark temperature tags**. When packing samples in the dry ice shipping box, place a tag in the biohazard document pouch of a kit at the bottom and top of the shipping box.
- Please always check HDClarity biokits **expiry dates** and do not use or discard expired itemsas replacements can usually be provided. Please contact CC to arrange replacements for expired components at least 14 days in advance. To ensure that relevant funds are always avaible for participant allowances, please remember to **request top ups to the travel support and stipend fund** at least quarterly or when the total falls below 50%.
- Please inform CC in advance of any exceptional cases, (e.g., where participants may require additional transportation, meals and/or lodging in excess of the allowances). ***Such requests must be approved before the visits***.

Thank you

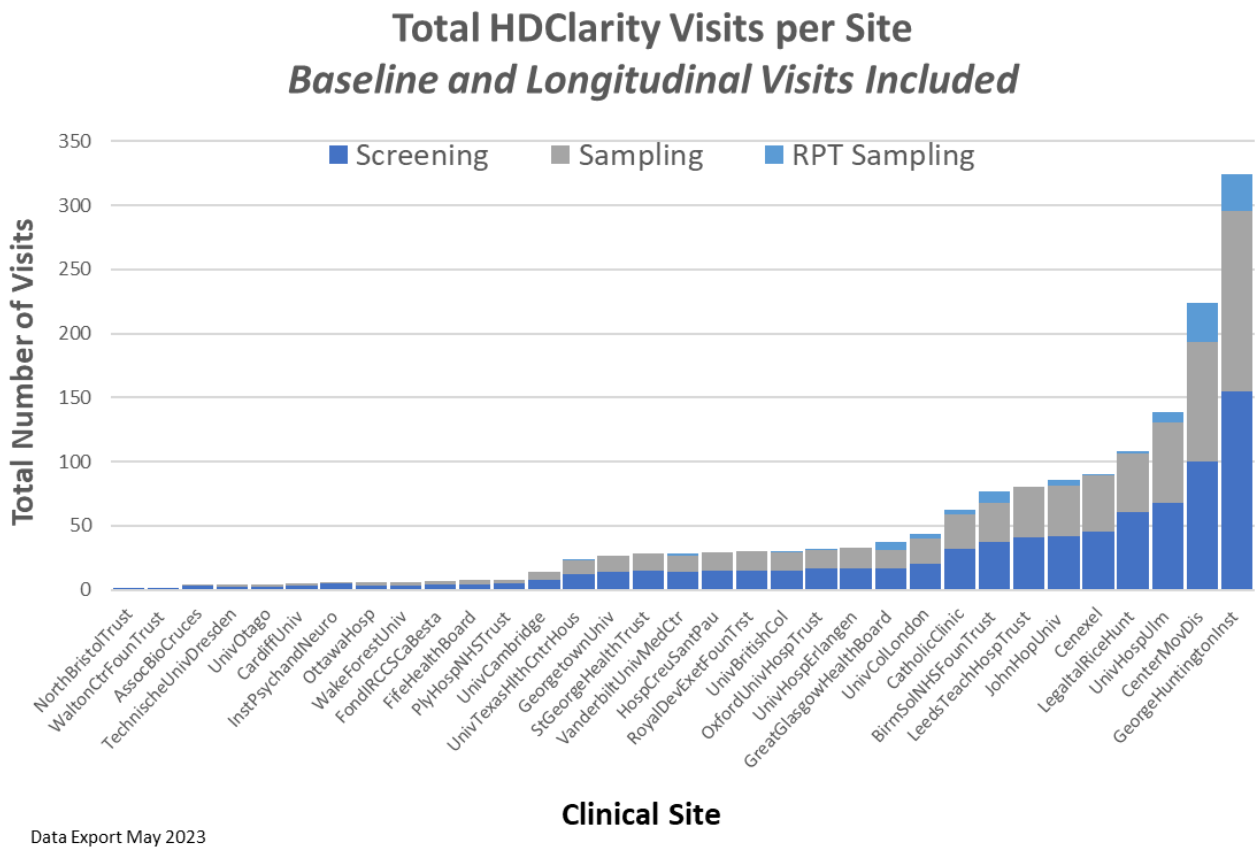
HDClarity Site Updates

HDClarity is active at 32 sites in 8 countries located across Australasia, Europe and North America (Figure 1). We would like to thank our newest sites at Ottawa Hospital, North York General Hospital and the University of Otago who have successfully enrolled their first participants into HDClarity!

Additionally, more sites have successfully transitioned to Protocol V4 (CLR4), with 10 sites having recruited participants into the longitudinal study. Many thanks to Professor Ferdinando Squitieri, and the team at Lega Italiana Ricerca Huntington (LIRH) and Dr Jee Bang and her team at St John's Hopkins University, who have transitioned to Protocol V4.

HDClarity Recruitment Updates

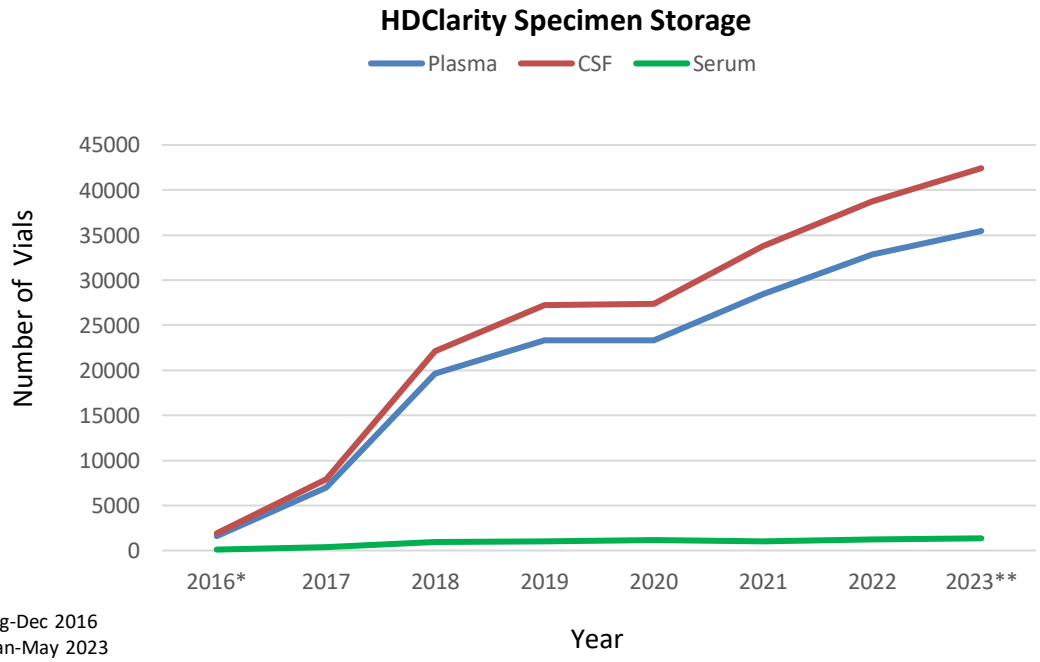
HDClarity sites have successfully competed 824 Screening Visits, 725 Sampling Visits and 111 Optional repeat (RPT) Sampling Visits. Since the previous edition (Oct 2022), you have completed an additional 90 Screening visits and 84 Sampling Visits. Thank you to everyone for your hard work and dedication over the last few months.



Recruitment under protocol V4 is also rising with University College London is currently leading the way with over 20 Y0 visits and the first Y1 Visit (Figure 2). This is closely followed by the Leeds Teaching Hospital Trust, University of Cambridge, and Vanderbilit University Medical Center.

Sample Collection

Due to the success of HDClarity there has been an increase in the number of CSF, plasma and serum samples in storage and available for research. Currently BioRep is storing 42419 vials of CSF, 35449 vials of plasma and 1354 vials of serum (Figure 3).



*Aug-Dec 2016
**Jan-May 2023

Research

The Huntington's Disease Therapeutics Conference 2023 was held in Dubrovnik, Croatia and showcased two key presentations using CSF and plasma samples from HDClarity.

Biofluid biomarker discovery in HD – Current possibilities and limitations

Niels Henning Skotte, PhD, University of Copenhagen

The genetic nature of Huntington's disease allows a precise diagnosis, but the use of biomarkers tracking disease progression as well as biomarkers responsive to treatment are essential to facilitate the development and evaluation of potential therapies for HD. This biomarker study explored several biofluids for novel protein biomarker candidates as well as substantiate previously identified protein changes. In addition, potential new targets of mechanistic and therapeutic interest for further exploration were identified. The recent proteomic results and findings from human CSF from healthy controls and HD gene carriers from the HDClarity cohort provided an overview of the most interesting protein candidates and their ability to track disease progression. The study highlighted the current possibilities and limitations for proteomic-based biomarker discovery as well as the important next steps to validate our findings and create scientific synergy within HD research.

Cholesterol and oxysterols as biomarkers for Huntington's disease?

William J Griffiths, PhD, Swansea University

Cholesterol and its metabolism are implicated in HD and recent studies indicate that gene therapy targeting cholesterol-related genes may offer a treatment for HD. The major oxysterol exported from brain is 24S-hydroxycholesterol (24S-HC), in human this is synthesized by the neuron specific enzyme cholesterol 24S-hydroxylase. Thus, 24S-HC in plasma represents a surrogate for cholesterol metabolism in brain. Using liquid chromatography the concentration of 24S-HC and other cholesterol metabolites in plasma and cerebrospinal fluid (CSF) from 400 HDClarity sample collections were determined. In plasma the concentration of 24S-HC is lower in manifest-HD than pre-manifest-HD or controls. In contrast, cholesterol is more abundant in manifest-HD than pre-manifest-HD. When both age and sex are considered as covariates 24S-HC is still significantly lower in plasma of manifest-HD patients than controls and almost significantly lower than in pre-manifest-HD patients. In contrast to plasma, oxysterol content of the CSF has two sources, brain cells and from the peripheral circulation by crossing of the BBB. Therefore, data from the CSF is more complex to interpret and analyses are currently ongoing.

Publications

Alterations in metal homeostasis occur prior to canonical markers in Huntington disease

Pfalzer, A.C., Yan, Y., Kang, H. *et al*. Alterations in metal homeostasis occur prior to canonical markers in Huntington disease. *Sci Rep* **12**, 10373 (2022).

The importance of metal biology in neurodegenerative diseases such as HD is well documented with evidence of direct interactions between metals such as copper, zinc, iron and manganese and mutant Huntingtin pathobiology. To date, it is unclear whether these interactions are observed in humans, how this impacts other metals, and how mutant Huntington alters homeostatic mechanisms governing levels of copper, zinc, iron and manganese in cerebrospinal fluid and blood in HD patients. Plasma and CSF from control, pre-manifest, manifest and late manifest HD participants were collected as part of HD-Clarity. Levels of CSF and plasma copper, zinc, iron and manganese were measured as well as levels of mutant Huntingtin and neurofilament in a sub-set of cerebrospinal fluid samples. Elevations in CSF fluid copper, manganese and zinc levels were altered early in disease prior to alterations in canonical biomarkers of HD although these changes are not present in plasma. CSF iron is elevated in manifest patients. The relationships between plasma and cerebrospinal fluid metal are altered based on disease stage. These findings demonstrate that there are alterations in metal biology selectively in the CSF which occur prior to changes in known canonical biomarkers of disease. This work indicates that there are pathological changes related to alterations in metal biology in individuals without elevations in neurofilament and mutant Huntingtin.