UCL

HDClarity

A multi-site cerebrospinal fluid collection initiative to facilitate therapeutic development for Huntington's disease

HDClarity Inaugural Investigator Meeting
EHDN Plenary Meeting, Bologna 2022

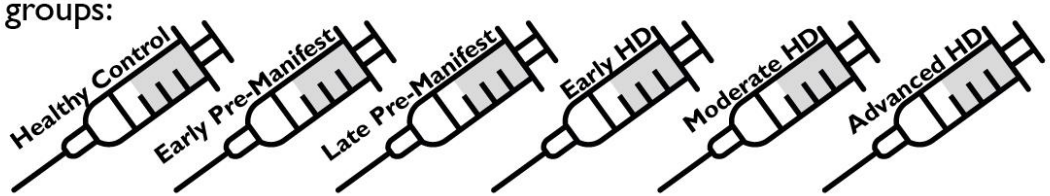
CHDI
Accelerating therapeutic development for Huntington's disease

HUNTINGTON'S DISEASE CENTRE

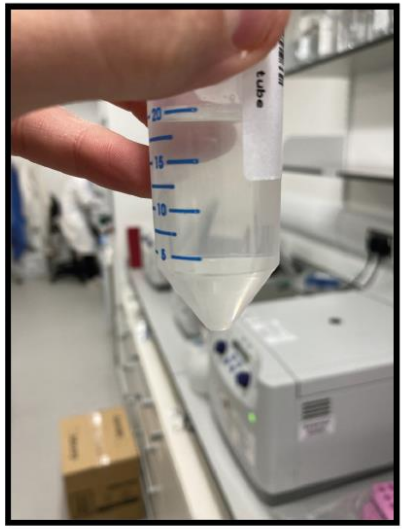
HDClarity Study Aims:

TO ADVANCE HD RESEARCH

COLLECT: We are building a collection of high-quality cerebrospinal fluid (CSF), plasma and serum samples across 6 study groups:



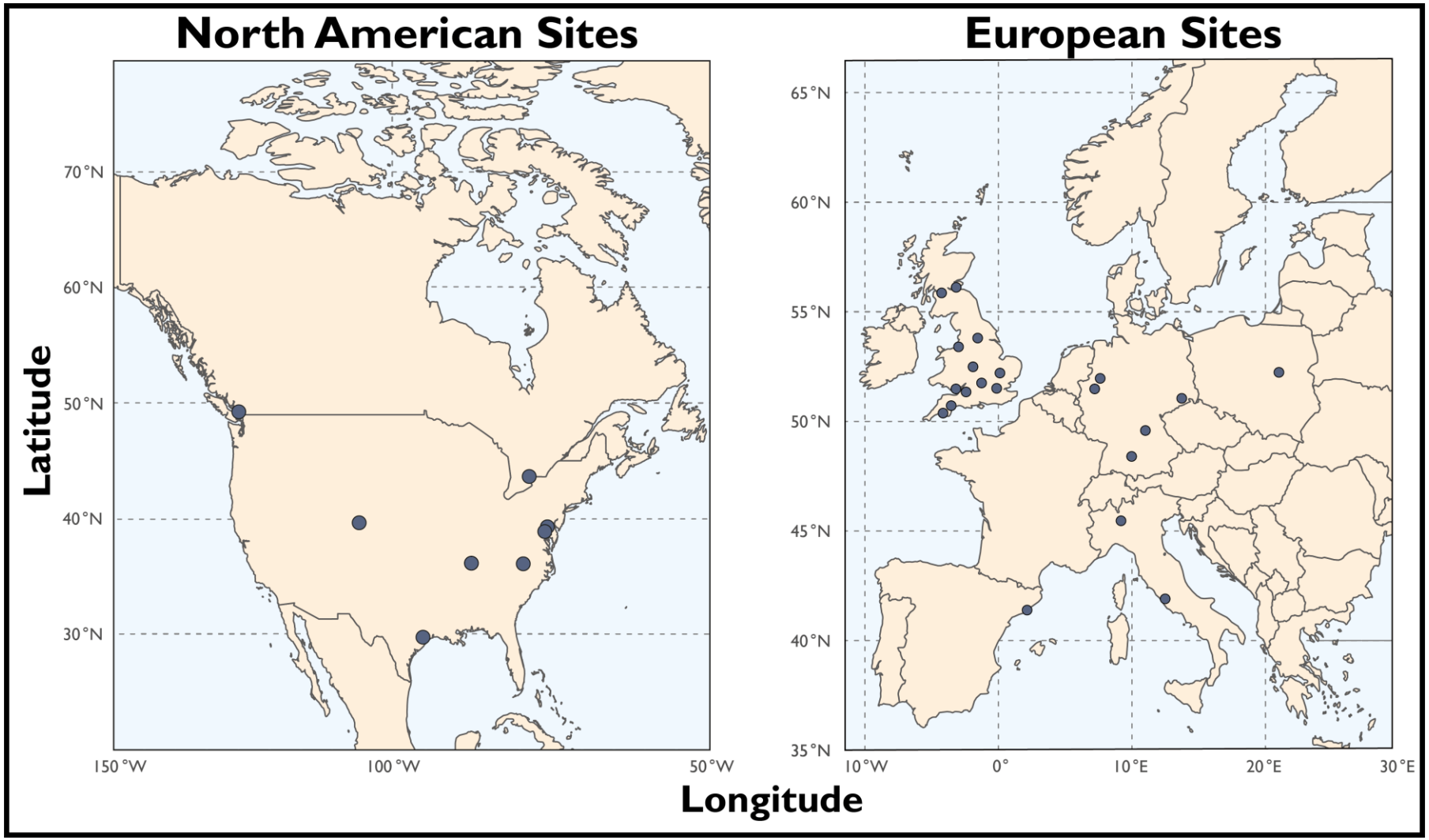
In total, over **12 Litres** of CSF have been collected worldwide!



DISTRIBUTE: Samples can be requested by investigators around the world, allowing them to conduct groundbreaking research to identify new biomarkers and develop treatments for HD.

1. Generate a **high-quality CSF collection** to evaluate **biomarkers** and **pathways** to enable development of **novel treatments** for HD.
2. Generate high-quality **plasma** sample collection matching the CSF collection
3. Collect **high-quality phenotypic data** for each participant using Enroll-HD core assessments
4. A minimum of **2500** participants

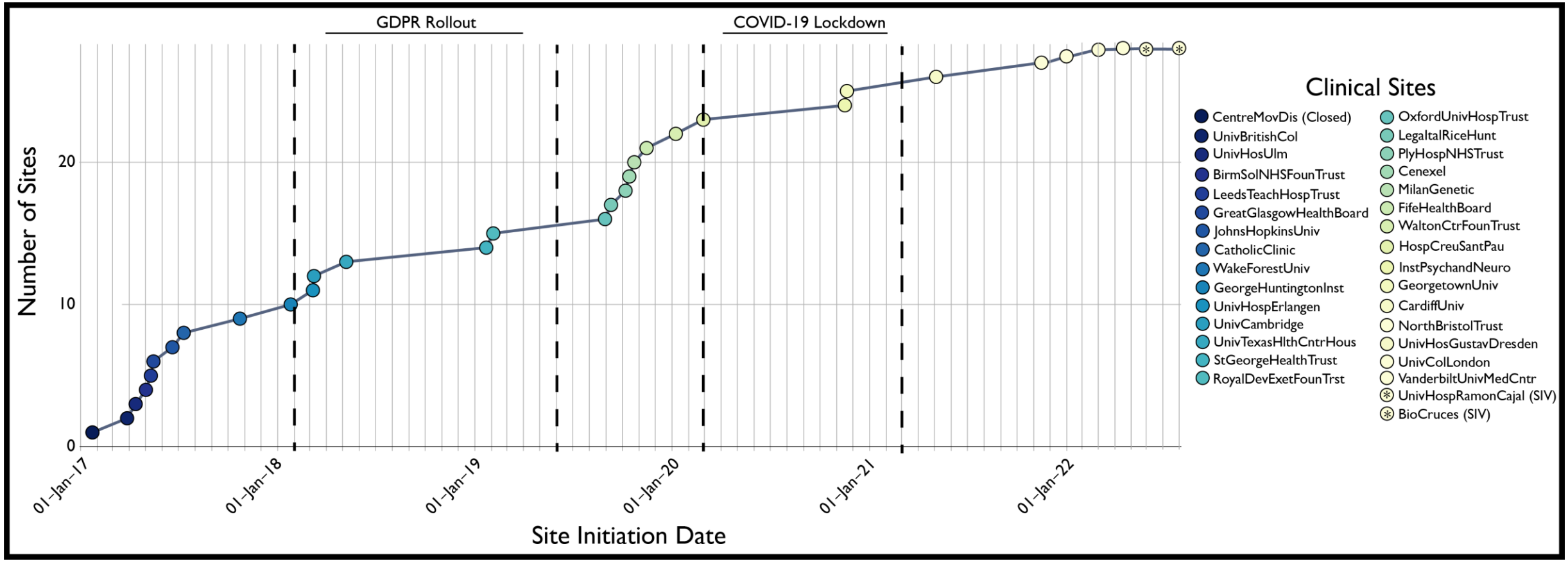
HDClarity Current Clinical Sites:



Country	Number of Sites
United Kingdom	13
United States	6
Germany	5
Italy	2
Canada	2 (1 active)
Poland	1
Spain	1

As of September 2022, we have **29** active clinical sites across **7** countries

HDClarity Clinical Site Initiation: Jan 2017 – Present:



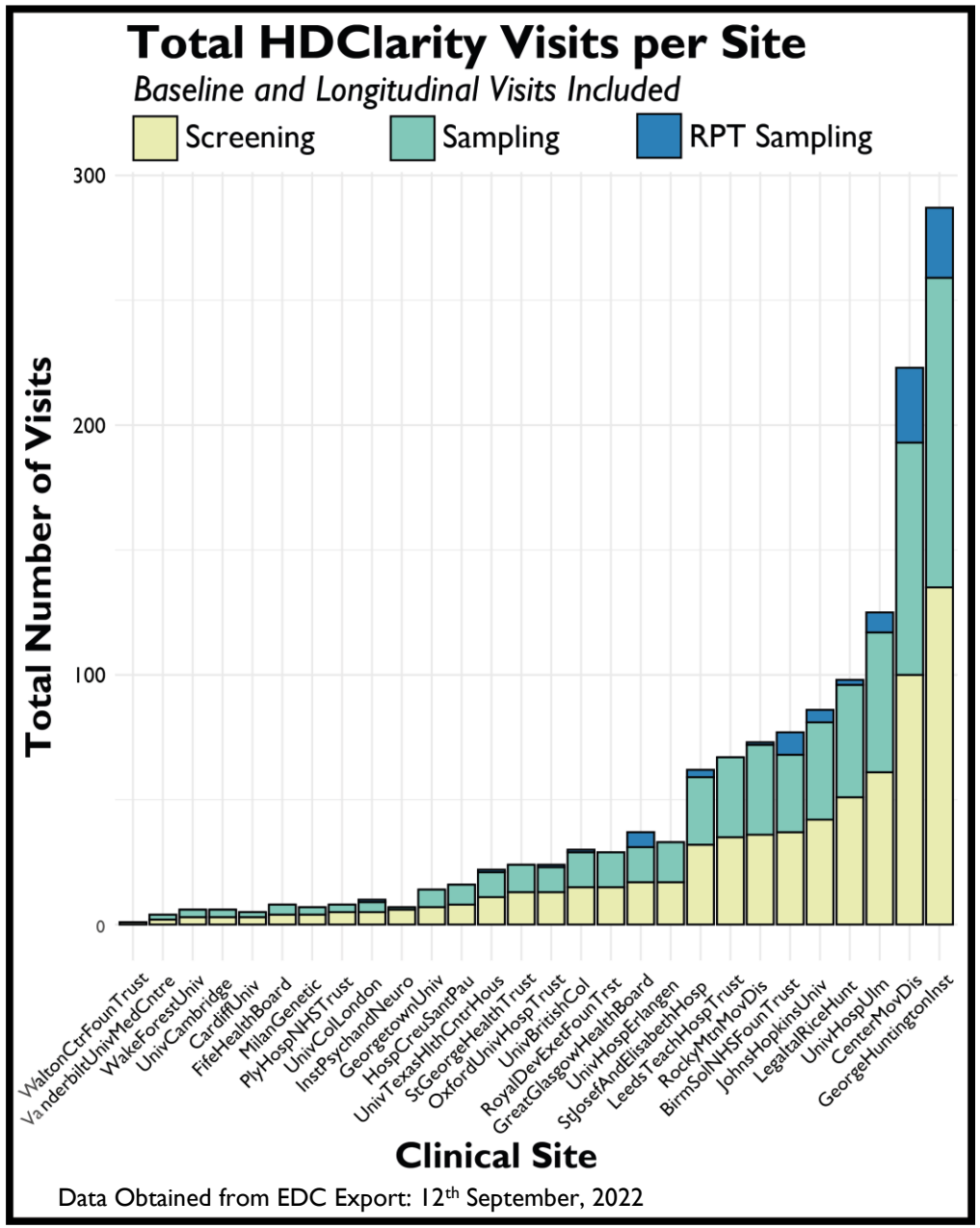
In 2022, we have successfully opened **3 new HDClarity sites** (UnivColLondon, UnivHosGustavDresden and VanderbiltUnivMedCntr), with a further **2 sites** having **completed their SIVs** (UnivHospRamonCajal and AssocBioCruces).

Additionally, **10 UK sites** are fully approved for **protocol v4,** with **5 of these sites** having started recruitment under the new protocol.

HDClarity Recruitment Across Sites:

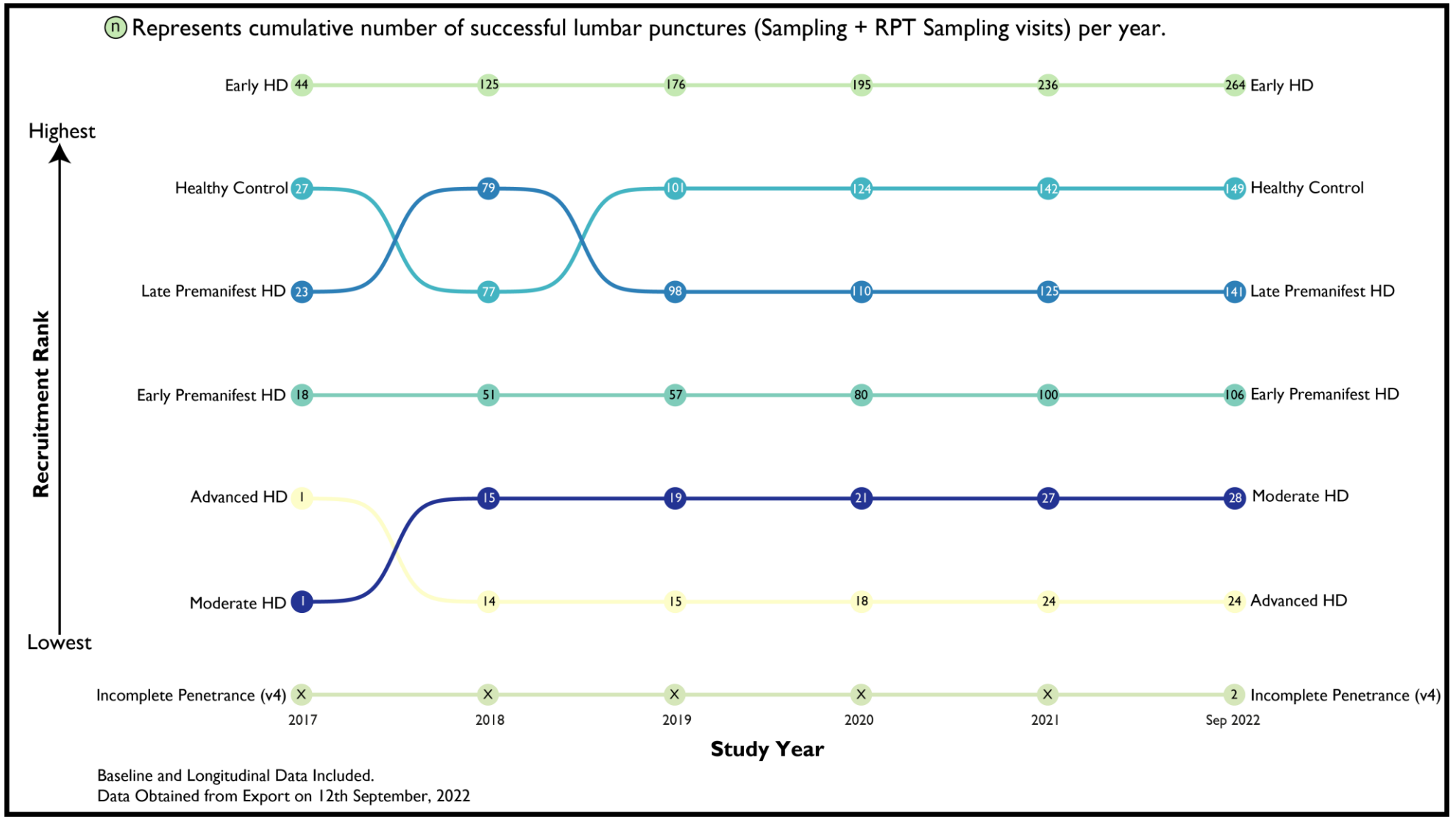
In total, we have now completed **688 Screening visits, 616 Sampling visits** and **98 Optional Repeat Sampling visits** across all sites, timepoints and protocol versions:

	CLR 2/3	CLR 2/3	CLR 4
Visit Type	Baseline Visits (% of total)	Longitudinal Visits (% of total)	Y0 Visits (% of total)
Screening	607 (88%)	69 (10%)	12 (2%)
Sampling	543 (88%)	63 (10%)	10 (2%)
Optional RPT Sampling	94 (96%)	1 (1%)	3 (3%)



Data Obtained from EDC Export: 12th September, 2022

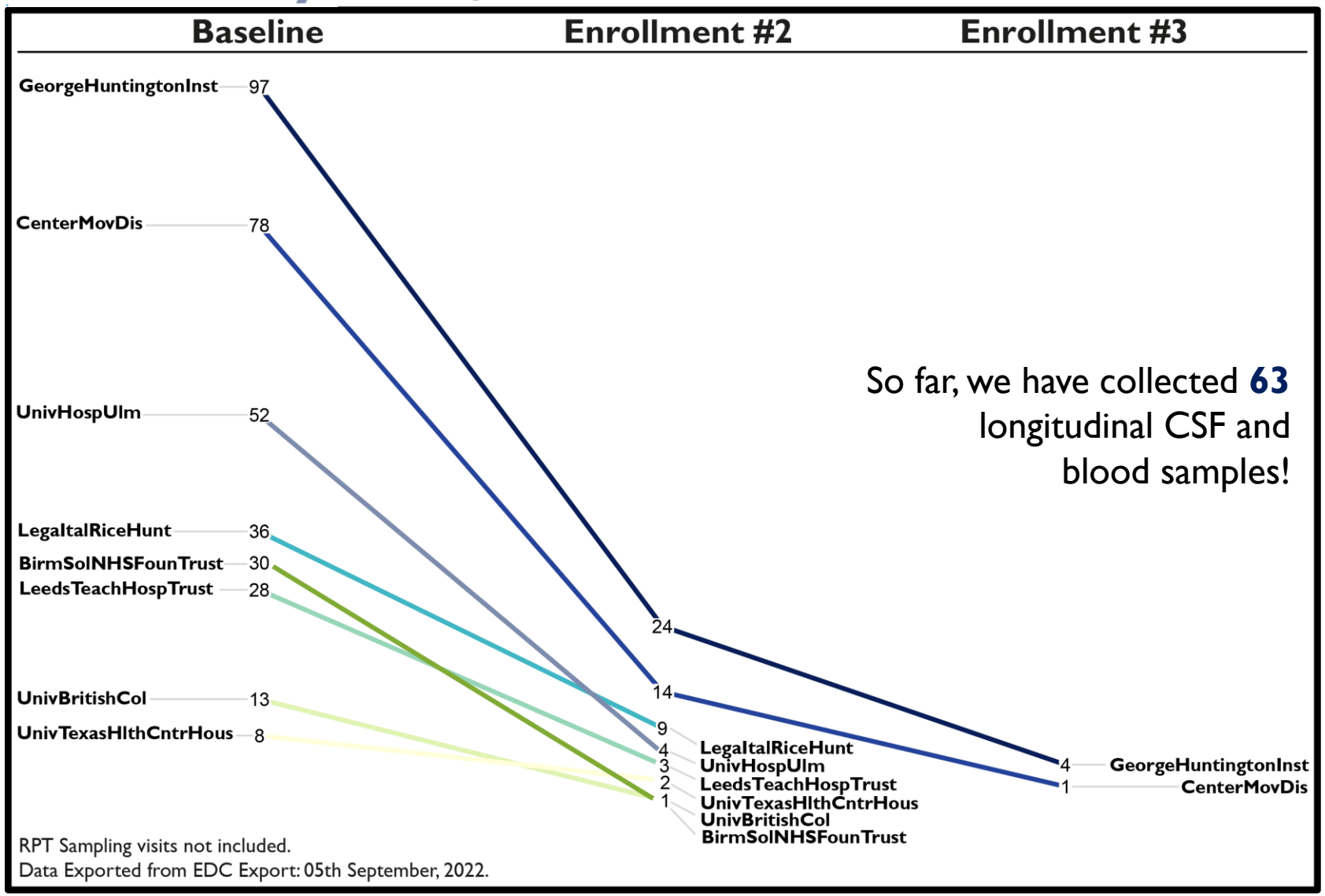
HDClarity Recruitment Across Participant Categories:



Across all study years, our highest recruiting participant category has been **Early HD,** accounting for **37%** of the total Sampling + Optional Repeat Sampling visits.

The 'Incomplete Penetrance' category has been introduced as part of Protocol v4, along with 'Juvenile HD'

HDClarity Longitudinal Recruitment in CLR 3:

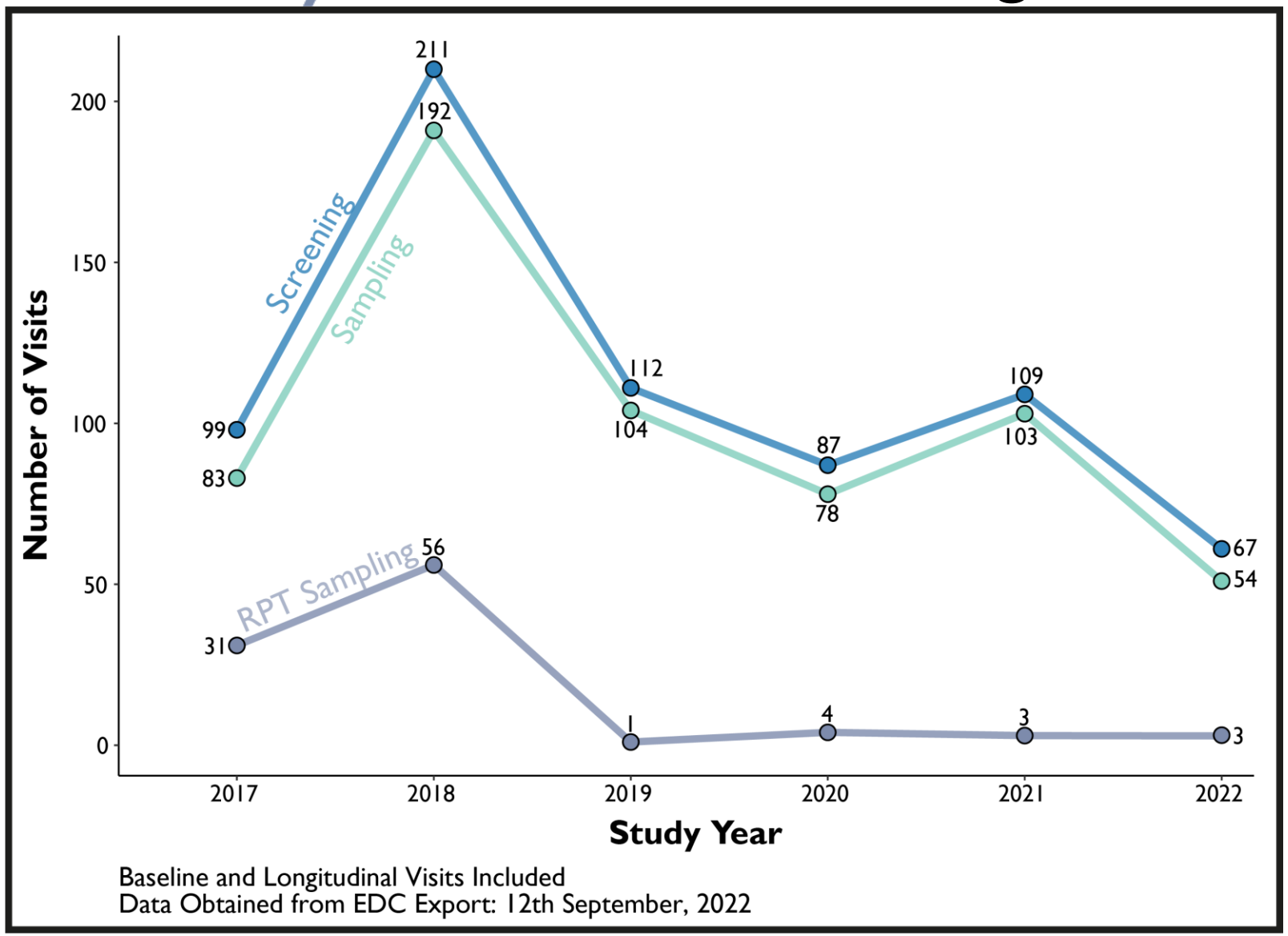


Site	Participants Returning (%)
GeorgeHuntingtonInst	24
CenterMovDis	18
UnivHospUlm	8
LegaItalRiceHunt	25
LeedsTeachHospTrust	11
UnivBritishCol	8
UnivTexasHlthCntrHous	25
BirmSolNHSFounTrust	3

Longitudinal samples are of critical importance in understanding how a **specific biomarker relates to disease progression**.

Cross-sectional data can sometimes **over-estimate true change** and result in misleading conclusions about the **prognostic potential** of the biomarker in being studied.

HDClarity Recruitment Challenges:



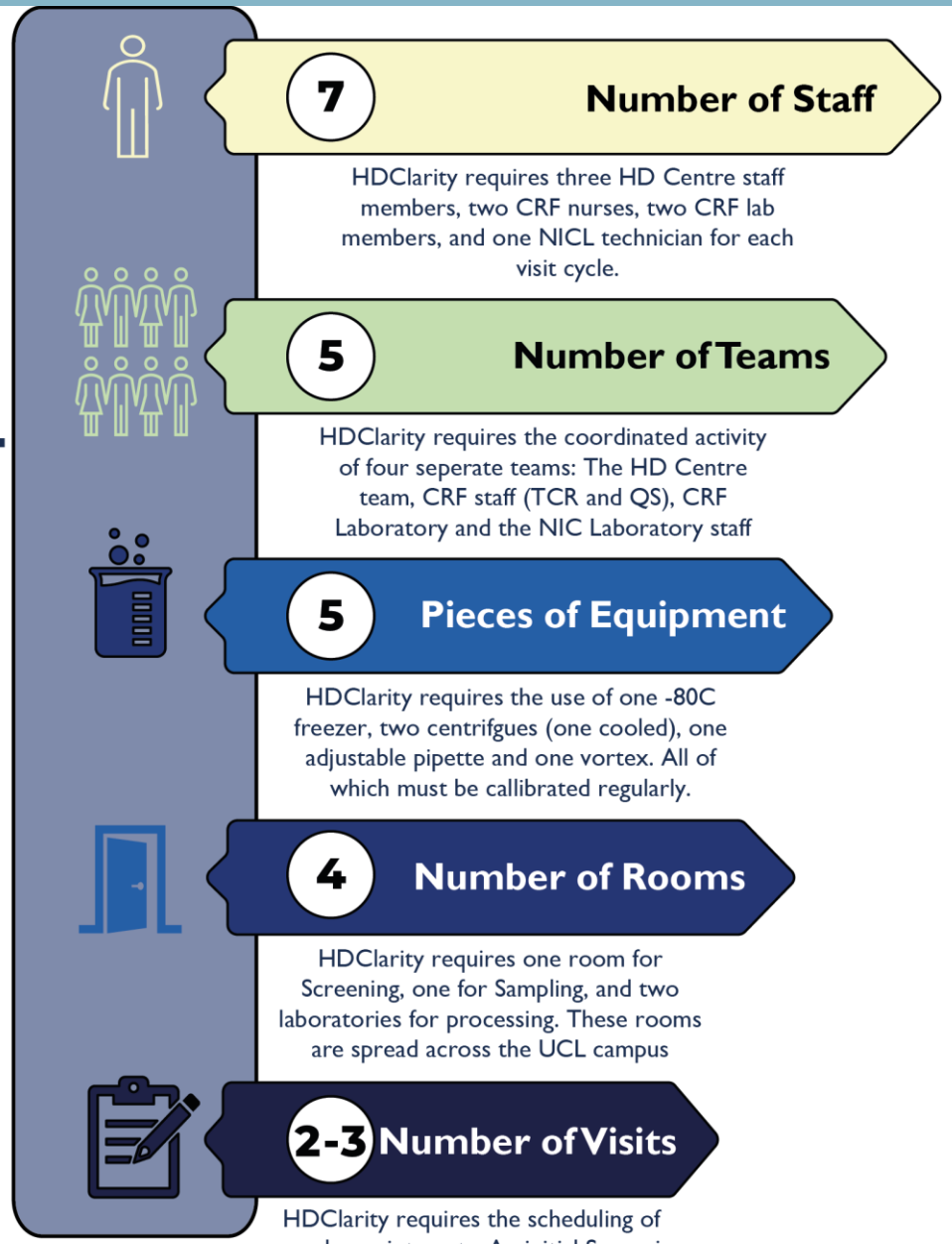
Recruitment in 2022 has been down compared to previous years, despite the efforts of clinical sites, central coordination and CHDI.

The COVID-19 pandemic continues to impact upon HDClarity, with the global **Omicron wave** forcing existing sites to **pause recruitment** due to a lack of capacity for the study. Additionally, a **complete retraining** is required for sites who have been inactive since the start of the pandemic.

Furthermore, the opening of new sites has been slowed by several factors common across multiple sites. These include:

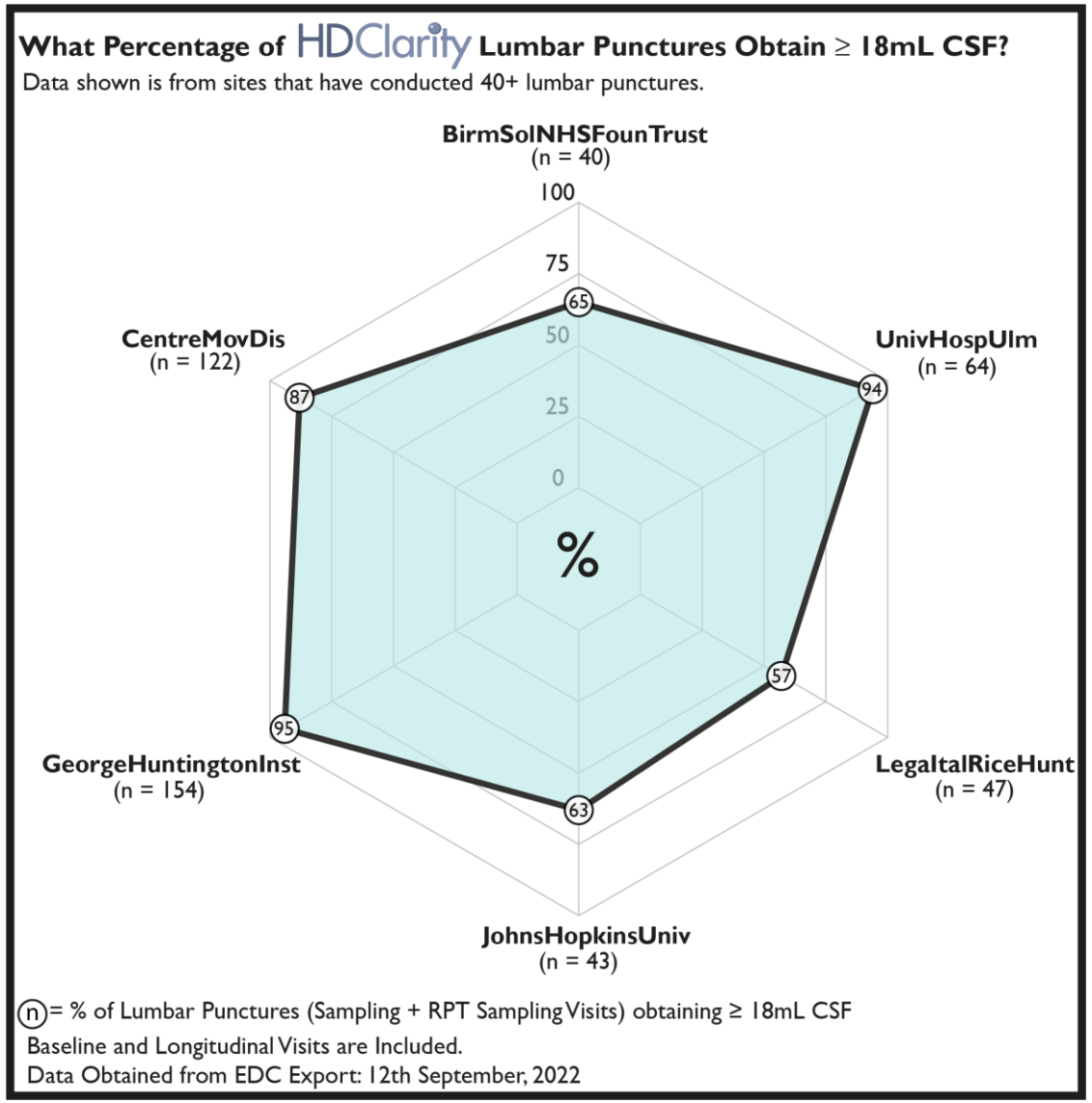
- Inability to perform **triplicate cell count** using the volume permitted by the protocol (200ul)
- **Lab equipment issues**, such as site centrifuges being unable to accommodate the 50ml CSF collection tube supplied in HDClarity kits
- **Sample processing cannot occur within the timelines** specified in the protocol
- **Delay in returning required documentation** to CC e.g., signed delegation/training log and calibration certificates.
- **Lack of CRF capacity** for any new studies.

HDClarity Resources Required



Despite its observational nature, HDClarity is a study that requires **multiple resources** and the **coordinated efforts of several teams** to run efficiently, ensuring the well-being of participants and the intergrity of sample quality.

HDClarity CSF Collection Summary:



HDClarity Lumbar Puncture Efficiency		
Protocol Version	CLR 2/3	CLR 4 Y0
Total Number of LPs	701	13
% LPs Obtaining ≥ 18ml	77 %	93 %

HDClarity LPs are **largely successful**; however, it is important to consider the following six points:

- Participants have **signed an ICF consenting to the collection of 20mls** and we have a duty to ensure the maximum scientific value from exposing volunteers to the risk from LP.
- The **minimum expected** CSF volume is **15ml**
- 20ml should be collected in every case unless there is a **specific technical or safety reason** why this cannot be done for a particular patient.
- The evidence shows that **collecting 20ml is not more likely to cause headache** than collecting smaller volumes.
- The use of **24G needles** is the best way to **reduce headache** risk.
- **No CSF** should be **retained** for local use

Under CLR 4, we now also obtain an accurate measurement of the **total volume of plasma** collected.

HDClarity Lumbar Puncture Safety Profile:

Research Report

Safety and Feasibility of Research Lumbar Puncture in Huntington's Disease: The HDClarity Cohort and Bioresource

Filipe B. Rodrigues[a], Gail Owen[a], Swati Sathe[b], Elena Pak[b], Dipinder Kaur[b], Anka G. Ehrhardt[b], Sherry Lifer[b], Jenny Townhill[c], Katarzyna Schubert[a], Blair R. Leavitt[d], Mark Guttman[e], Jee Bang[f], Jan Lewerenz[g], Jamie Levey[b,c] for the HDClarity Investigators, Cristina Sampaio[b] and Edward J. Wild[a,*]

[a]*UCL Huntington's Disease Centre, UCL Queen Square Institute of Neurology, London, UK*
[b]*CHDI Management/CHDI Foundation, Princeton, NJ, USA*
[c]*Enroll-HD platform, European Huntington's Disease Network, University Hospital of Ulm, Ulm, Germany*
[d]*Centre for Molecular Medicine and Therapeutics, Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada*
[e]*Division of Neurology, Department of Medicine, University of Toronto, Toronto, ON, Canada*
[f]*Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA*
[g]*Department of Neurology, Ulm University, Ulm, Germany*

AE Reported	Frequency (%)
Headache	90 (47)
Backpain	54 (28)
Fainting	10 (5)
Nausea/Vomiting	7 (4)
Bruising	7 (4)
Paraesthesia	2 (2)
Other	19 (10)

- **118 (62.43%)** were mild
- **70 (37.04%)** were moderate
- **1 (0.53%)** was severe

- **572 LPs = 189 AEs** across **138 visits** (24%).
- Headache was most common AE and typically resolved within a few days
- **1 SAE** reported (0.17%) – Blood patch required after prolonged, moderate headache
- Manifest HD had numerically **fewer** AEs that HCs. No difference between PreHD and HC
- Age, gender, BMI or DBS were **not associated** with occurrence of AEs in gene expansion carriers.
- Research LPs in HD are **feasible** and **acceptable** to the community, and have a **manageable safety profile**

HDClarity Biosample Distribution and Usage:

- The Scientific Review Committee has so far reviewed and approved over **15 HDClarity sample requests**

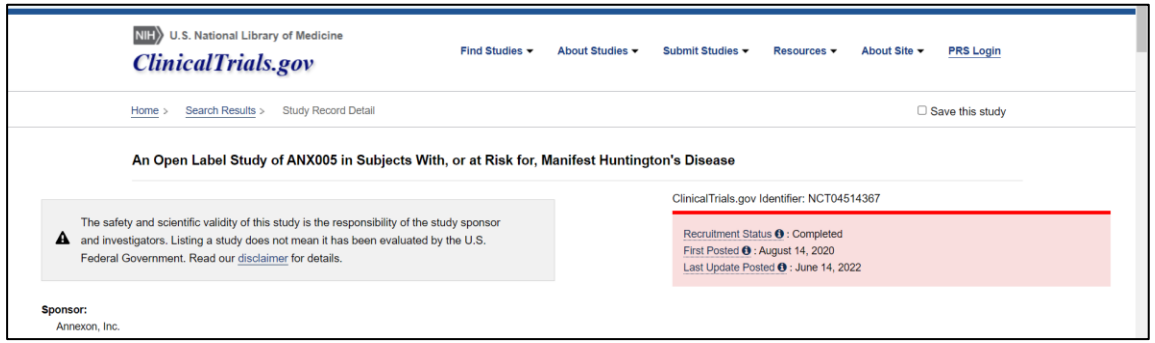
Biofluid	Cryovials Shipped
CSF	3251
Plasma	2662
Serum	238

Rodrigues et al., 2022

- The samples have been used in the **validation** of biomarkers and/or assays, **proteomic discovery** of new HD biomarkers and **evaluation** of novel proteins

Recently, HDClarity samples have been used in a **'SomaLogic Analysis'** allowing researchers to measure **7000 proteins** in CSF. This is an amazing achievement and a huge step forward for the discovery of new biomarkers!

Additionally, our samples have been used to explore the role of the **compliment system in HD** pathogenesis, the results of which have helped shape **new clinical trials** conducted by Annexon Bioscience!



HDClarity 2022 Successes:

HDClarity Management Team: UCL

UCL Central Coordination	Study Role
Professor Ed Wild **Chief Investigator**	Executive oversight and oversees all study management activities.
Dr Gail Owen **Study Manager**	Management of the conduct of the study and responsible for all study documents.
Dr Seema Maru and Dr Kat Schubert **Study Coordinators**	Management of site assessment and initiation processes, site training, management of active sites, disbursement reports.
Mr Alex Lowe **Research Assistant**	Remote data monitoring and review of onsite monitoring. Maintains the kit tracker, recruitment tracker, EDC study information, equipment calibration and lab certification.
Dr Sankaranarayanan Ramachandran **Quality Control Officer**	Advises on all clinical/technical matters (lab manual, biosample kits, LP procedure, CSF collection, sample processing)
Ms Mara Terres Rodriguez **Study Administrator**	Provides administrative support (financial management, study master file, meetings) and assists with progress and disbursement reports, greenlight requests and study websites.

HDClarity Management Team: CHDI

CHDI Project Management	Study Role
Eileen Neacy	Chief Operating Officer
Swati Sathe, MD	Medical Vice President and HDClarity Medical Monitor
Sherry Lifer	Director, Contract Finance and Operations
Hilary Wilkinson, PhD	Director, Clinical Wet Biomarkers
Shilpa Deshpande Director, Clinical Operations	Management of HDClarity EDC access, oversight and point of escalation for EDC management and Greenphire vendor management.
Elena Pak Study Lead	Management of study, MRO agreement and service agreements with third parties, Greenphire payment authorization, ICFs, site agreements and site pricing.
Kiran Borkar and **Patrick Sicilia** Clinical Programme Managers	Preparation of site agreements and ICFs, communication with third parties and assist with payment authorization and study management.
Jamie Levey Clinical Platform Co-Leader	Oversight of study start-up, site assessments, study conduct and maintenance
Julia Keklak CPM - Biorepository	Oversight of HDClarity biokit set up, stock, ordering and delivery
Olivia Handley Enroll-HD Global Project Manager	Facilitating the development of the HDClarity EDC, communication between HDClarity study team and Enroll-HD management team.