

Review Date	Last Name	First Name	Institution	Title	Cohort	Abstract
2013	Hersch	Steven	Harvard Medical School	Blood levels of soluble and aggregated mutant huntingtin: Biomarkers for PreManifest Huntington's disease progression	PREDICT-HD	Huntington’s disease (HD) is caused by the cellular expression of the toxic mutant huntingtin protein (mtHtt). mtHtt misfolds, oligomerizes, and becomes insoluble forming intracellular aggregates which are a pathologic hallmark of the disease. Both the soluble and aggregated forms of mtHtt are important for the understanding of disease progression and the response to therapeutic agents modulating mtHtt. While the soluble form of mtHtt may be the most toxic, aggregates have been documented to correlate with disease onset in mice. (Baldo et al) Many of the current efforts for developing neuroprotective therapies for HD target mtHtt directly or indirectly and are aimed at huntingtin translation (siRNA and oligonucleotides), misfolding, cleavage, post-translational modifications, aggregation, or clearance and therapeutic leads for all of these are in development. Assays currently used for preclinical and clinical studies of treatments affecting mtHtt only detect soluble protein and leave unanswered questions about whether the intervention might reduce one or both forms or cause a shift between forms. Having reliable mtHtt markers able to distinguish and measure the soluble and aggregated forms of mtHtt is crucial for understanding the effect of therapeutic regimens on these pathologic moieties.
2014	Schulman	Howard	Caprion Proteomics US	Integrated approach to protein biomarker identification in Huntington’s Disease	PREDICT-HD	Mass spectrometry-based approaches for protein biomarker discovery and validating offer a new perspective for clinical pathology at the molecular level. In an effort to find biomarkers of Huntington’s Disease, strategic application of such proteomic approaches to PREDICT-HD samples is proposed. The Caprion proteomics platform, with integrated and robust processes including sample processing, data acquisition and analysis, biomarker candidate prioritization, assay development and biomarker validation, will be utilized. A combination of unbiased differential profiling technologies followed by targeted multiplexed assays for validation of the initial findings will be used. Initial discovery studies are planned on the available plasma samples to compare cohorts representing non-carriers and carriers grouped as early progression and late progression by their CAG-Age Product (CAP) scores. The 3 cohorts (control, early progression and late progression) would each be followed over time with sampling at 3 time points in the discovery phase to find markers of disease progression. A cohort of symptomatic subjects will also be analyzed for comparison. In the validation phase, the time points will represent yearly progression of disease as smaller changes will be accessible for analytical measurements and may be of greater clinical use.
2014	Scherzer	Clemens	Brigham and Women's Hospital	A Next Generation of Biomarkers for Incipient Huntington's Disease	PREDICT-HD	Early intervention will be instrumental to slow or even prevent the clinical manifestations of Huntington’s disease (HD). To enable early intervention, biomarkers are needed that track disease processes before devastating symptoms develop. Multiple lines of evidence implicate mutant huntingtin-induced transcriptional dysregulation of messenger and microRNAs in the disease pathobiology. Although HD symptoms reflect preferential neuronal death mutant huntingtin is ubiquitously expressed and biochemical changes can be found in peripheral cells and fluids. This creates an opportunity for translation into clinically useful biomarkers. We hypothesize that microRNAs and messenger RNAs can serve as cerebrospinal fluid and blood markers that track the progressive disease process – before the clinical phenotype manifests. Next-generation sequencing of microRNA transcripts offers advantageous precision, dynamic range, and sensitivity compared to traditional

						analog gene expression platforms. Here we will use massively parallel sequencing to discover and independently replicate all known and novel microRNA transcripts associated with pre-manifest HD in cerebrospinal fluid and blood of 100 cases and 100 age- and sex-matched controls. Replicated cerebrospinal fluid and blood microRNA markers will then be translated onto digital, go-to-the-clinic assay platform. Furthermore, messenger RNAs previously linked to manifest HD will be evaluated for use as potential peripheral biomarkers in individuals at pre-manifest disease stages. To build a generally useful launch platform for biological markers of incipient HD we will establish a cerebrospinal fluid and blood RNA biobank linked to PREDICT-HD – a national resource for the development of molecular markers designed to guide treatment of onset disease. This study will discover and replicate biofluid transcripts potentially useful for monitoring disease processes prior to the onsets of clinical symptoms. If confirmed, this next generation of biomarkers will transform clinical trial design and will enable earlier and more effective intervention.
2014	Jones	Dean	Emory University	Metabolic dysfunction in Huntington disease	PREDICT-HD	Growing evidence points to metabolic dysregulation as a primary and early feature of HD. While classic HD motor and cognitive symptoms likely contribute to weight loss in later stages of the disease, they do not fully explain the weight loss, lower BMI, and slower rates of weight gain observed among early and especially pre-symptomatic patients. Differences in metabolism may be occurring even during development: a recent anthropometric analysis among 7-18 yr old children at risk for HD (but without manifest symptoms) found those with expanded CAG repeats exhibited smaller mean head circumference (adjusted for height), BMI and weight measurements than healthy controls. Post-hoc analyses of expanded CAG carriers split by age extremes found those aged 13-18 had significantly lower BMI than healthy controls, while ages 7-12 were not significantly different⁶. There is accumulating evidence of defective metabolic function at early stages of disease. HD patients are in negative energy balance and exhibit higher total energy expenditure (TEE), though it is unclear why: higher TEE correlated with increased physical activity in two studies but was not correlated with chorea or other motor scores in another. Higher fasting energy expenditure, higher lipid oxidation rates and a larger rise in post-insulin-challenge glucose oxidation are also observed among early stage HD patients. Pre-symptomatic patients had significantly lower plasma branched-chain amino acids, which negatively correlated with CAG repeat length. These data may suggest a pro-catabolic metabolic state occurs before motor symptoms and may worsen in a polyglutamine-tract dependent fashion. Lower BMI, faster rate of weight loss and higher caloric intake correlate with longer CAG repeat length in HD patients, suggesting that mutant huntingtin is involved in metabolic dysregulation. Metabolism is one of the most poorly understood aspects of HD. Initial attempts at metabolomic characterization of HD have generated intriguing evidence of an early pro-catabolic shift in metabolic balance. A gas chromatography time-of-flight mass spectrometry (GC-MS) analysis of early and presymptomatic HD (n=30) tentatively distinguished HD from controls on the basis of metabolites linked to increased nucleic acid breakdown, fatty acid-oxidation and possibly amino acid turnover. A recent ¹H-NMR metabolomics study in yeast expressing mutant huntingtin N-terminal fragments identified 11 altered metabolites. Four of these (alanine, glutamine, glycerol and valine) corresponded to published findings from human and murine model analyses, demonstrating systemic alterations in protein and fat metabolism associated with mutant huntingtin. Reduced branched chain amino acids

						were also separately detected in ^1H-NMR analysis of HD patients' plasma, and correlated with CAG repeat length. Altered metabolic signatures have also been found in transgenic and toxin animal HD models. The PREDICT-HD study has collected annual blood, urine and cerebral spinal fluid samples in over 1300 premanifest research participants for up to ten years. The sample is well-characterized phenotypically in concert with every sample acquisition. These data have not yet been used to examine metabolic processes in HD. PREDICT-HD data allow a unique opportunity to greatly improve the understanding of metabolic pathways in the pathogenesis of human HD.
2015	Potkin	Steven	University of California-Irvine	CSF-enhanced-aggregation Biomarker for Parkinson's Disease	PREDICT-HD	CSF biomarkers have been the subject of a number of investigations. A proteomic profile revealed increased prothrombin, apolipoprotein A-IV, and haptoglobin in CSF of HD patients compared to controls. The ration of CSF prothrombin/albumin was elevated and significantly correlated with the UHDRS. However, other studies have found CSF markers of inflammation, elevated in most neuro-degenerative disease and not specific to HD. A similar lack of specificity is also demonstrated for increased F2-isoprostane, an inflammatory marker that is increased in CSF, urine, and plasma of both HD subjects and Alzheimer's subjects. A lack of specificity has also been shown for CSF and plasma GABA as well as non-specific elevations in CSF light subunit of neurofilament triplet protein. However, NFL elevations were correlated
2015	Myers	Richard	Boston University School of Medicine	Epigenetic Markers in Huntington Disease Brain	PREDICT-HD	As part of our study of epigenetic regulatory mechanisms in Huntington's disease, we have performed microRNA-sequencing in 28 HD brain samples and 36 control brains samples in the prefrontal cortex. We have identified several microRNAs that are strongly associated with the extent of pathological involvement in the striatum in HD brains, and some of these are also related to the size of the CAG repeat size and CAG-adjusted age at onset. Because microRNAs are known to be stable in biofluids, and because past studies of Parkinson's disease CSF detects the same microRNAs implicated in our Huntington's disease studies, we believe that these microRNAs may be valuable biomarkers of neurodegeneration in HD. This work was recently accepted for publication in BMC Medical Genomics (Hoss et al. miR-10b-5p expression in Huntington's disease brain relates to age of onset and the extent of striatal involvement. BMC Medical Genomics, in press). While our NIH/NINDS proposal below focuses on examining blood biomarkers, the analysis of microRNAs in blood and CSF has indicated that brain levels of microRNAs are much more strongly related to CSF levels than blood levels. Thus we are seeking to evaluate the relationship of these microRNAs to disease state in CSF and to the proximity to onset among HD presymptomatic gene carriers.
2015	Dai	David	Oxford Nanopore Technologies	Research in Sequencing DNA for Diagnosis of Huntington's Disease	PREDICT-HD	
2015	McDonald	Marcy	Massachusetts General Hospital	Genetic Modifiers of PREDICT-HD Phenotypes	PREDICT-HD	Huntington's disease (HD) is caused by a CAG expansion mutation whose length is the primary determinant of the age at which diagnostic motor signs emerge, typically in mid-life. The length of the CAG repeat is also correlated with age of onset of cognitive or psychiatric clinical signs in those who present first with these features. Thus, CAG repeat length influences the rate with which biological changes in HD that begin early, due to the expression of mutant huntingtin, lead much later to motor, cognitive or psychiatric onset, although not all steps in each of these three pathogenic processes are

						likely to be identical. However, the age at onset of motor signs, and likely the timing of cognitive, psychiatric and imaging abnormalities, is influenced by other as yet unidentified genetic factors, not as independent risk factors but as modifiers, i.e., suppressors or enhancers of phenotypes dependent on the presence of an expanded CAG repeat. PREDICT-HD, which was established as an observational study to investigate the effects of the HD mutation during the decades prior to diagnosis, has accumulated a wealth of data in various domains, including brain imaging, motor signs, cognitive disturbance and psychiatric manifestations, that represent a valuable resource for identifying potential modifiers. Via the Center for Inherited Disease Research (CIDR), we have recently generated genome-wide SNP data for PREDICT-HD, and we have complemented these data with genome-wide SNP data for more than 6,000 HD individuals from the Huntington Study Group COHORT study, the European Huntington Disease Network's Registry study and a collection of banked post-mortem HD brains. A coordinated strategy using PREDICT-HD in combination with these other datasets offers the opportunity to identify genetic modifiers that influence the disease pathway(s) triggered by the HD mutation by enhancing or suppressing its timing and/or modifying its phenotypic expression. To identify genetic factors that alter the course of HD, we will use a combination of genome-wide association (GWA) analysis of common variants to quantitative HD phenotypes and analysis of rare SNPS identified by whole exome sequencing of 'extreme' individuals whose phenotypes differ substantially from those expected from their CAG-length and age. Completion of our aims will advance HD research toward effective therapeutics, as the identification of modifier genes, which alter the rate or expression of the disease in human patients, could provide 'pre-validated' targets for therapeutic development as well as a new tool for stratifying clinical trials to maximize their informativeness.
2016	Yang	Xiangdon	University of California-Los Angeles	Validating NT17 Dependent Mechanisms in Huntington's Disease Suppression	PREDICT-HD	Huntington's disease (HD) is a dominantly inherited genetic disorder characterized by neurodegeneration of predominantly striatal medium-sized spiny neurons and cortical pyramidal neurons. Neuronal dysfunction and neurodegeneration in HD leads to motor dysfunction, psychiatric symptoms, cognitive decline, and eventually death 15-20 years after the onset of clinical symptoms. A hallmark feature of HD is the aggregation of expanded polyglutamine Huntingtin protein in the brain as a result of the causal CAG repeat expansion in the HTT gene. Recent work on Alzheimer's and Parkinson's diseases has shed light on the pathogenic phenomenon of aggregate seeding and spreading, in a prion-like fashion, in those diseases, and preliminary evidence of the ability for cultured cells to take up Huntingtin aggregates has been published. Despite this, there is still not evidence that aggregated Huntingtin can undergo intercellular propagation to seed aggregation in new cells. In this supplement, we aim to test the hypothesis that mutant Huntingtin protein aggregates can propagate from cell-to-cell to seed aggregation. We will test our hypothesis using a novel chambered cell culture system and using in vivo transplantation of Huntingtin aggregates in HD mouse models. With the recent findings determining the significance of aggregate propagation in other neurodegenerative diseases, our findings may contribute to the recognition of a common pathogenic mechanism linking these diseases. Finally, the discovery of a new pathogenic mechanism in HD would lead to new avenues for potential therapeutic intervention, one that could possibly be utilized for other neurodegenerative diseases that feature the spreading of aggregate proteins.

2016	Gigley	Jason	University of Wyoming	Interaction between neuroinflammation and neurodegeneration studied using latent Toxoplasma gondii infection in a mouse model of Huntington's disease	2CARE	Huntington's disease (HD) is caused by a CAG repeat expansion in the HTT gene. However, environmental factors impact onset of HD in people carrying the disease mutation (Wexler, N.S. et al. PNAS 2004). Environment could explain variability in age of onset, rate of progression and the spectrum of disease signs. An important environmental factor that may have an affect on HD is neurotropic infection. We have very strong preliminary data and a published manuscript (Donley, D.W. et al PLoS ONE 2016) demonstrating that an interaction occurs between a neurotropic infection Toxoplasma gondii and Huntington's disease in a mouse model. In unrelated independent studies the rate of people seropositive for Toxoplasma gondii infection in the same region where Venezuelan HD cohort lives is 41.8---53.5 % (Diaz---Suarez, O. et al., Rev Inst Med Trop Sao Paulo 2009). Worldwide prevalence of this parasite is on average 30% of the human population and infection is life long. T. gondii infection is correlated with depression, anxiety, bipolar disorder and suicide in humans (Nimgaonkar, V.L. et al. Schizophr Bull. 2012), all of which can occur in phenoconverted HD patients. Based on the coincidence of HD and T. gondii in the human population and our previous studies we hypothesize that T. gondii is a neurotropic infections that impacts age of HD onset. Therefore, we are Interested in testing HD patients for the presence or absence of antibodies against T. gondii and determining if being seropositive impacts age of onset after correction for CAG expansion size. We propose to obtain plasma samples from HD patients and test them for the presence of antibodies against Toxoplasma gondii using a commercial clinical ELISA kit used to diagnose T. gondii infection. We will then determine if there is a correlation between being seropositive for the parasite and age of HD onset, HD progression or HD severity using clinical assessment data matched to each patient sample.
2017	Boyanapalli	Ramakrishna	Wave Life Sciences	Application to HD-BRAC requesting the access to CSF samples from HD patients	PREDICT-HD	Wave Life Sciences has initiated PRECISION-HD1 and PRECISION-HD2, Phase 1b/2a multicenter, randomized, double-blind, placebo-controlled studies to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and multiple doses of WVE-120101 and WVE-120102 in adult patients with early manifest Huntington's Disease (HD) who carry a single nucleotide polymorphism (SNP) rs362307 (SNP1) and rs362331 (SNP2). Wave Life Sciences is currently qualifying a PD biomarker assay to measure mHTT protein in CSF for clinical trial use. The established LLOQ of the assay under optimization is in femtomolar range. However, it has been known that in addition to full length mHTT protein, many fragments of the protein may be present, and all forms of mutant huntingtin are not alike (different chain lengths) thus the assay performance for these fragments need to be established. We currently have limited understanding of quantities of mHTT protein present in CSF of HD cross-sectional population as well in a longitudinal study and the change or correlation with disease progression given limited availability of CSF samples from HD patients. Access to HD patient CSF biosamples will help us evaluate above parameters and establish acceptance criteria for the biomarker assay to assess the response of the investigational drugs on the levels of mHTT reliably.
2017	Chelsky	Daniel	Caprion Proteomics US	Integrated approach to protein biomarker identification in Huntington's Disease	PREDICT-HD	Huntington disease (HD) is an autosomal dominant fatal neurodegenerative disorder leading to an inexorable decline in motor, cognitive and behavioral functions over 30 years. There is currently no cure and the few treatments available are for symptom modification. One of the obstacles to an acceleration of treatment studies for HD is a lack of biomarkers that can efficiently identify and track

						disease. The PREDICT-HD study allows an unprecedented opportunity for the discovery and validation of markers tracking HD. PREDICT-HD is a longitudinal study designed to characterize clinical and biological markers of HD in participants prior to the manifestation of the full clinical phenotype. Over the past decade findings from this study have documented early markers of cognitive, motor, behavioral, psychiatric, functional, and brain changes at least 15 years before a traditional clinical diagnosis is made. Despite progress in the documentation of the natural clinical course of HD, fewer advances have occurred in the development of wet biomarkers. The identification of a biomarker that can provide reliable and valid measures of disease-related changes in HD could accelerate the search for treatments. Importantly for the development of putative disease-modifying drugs for HD, biomarkers might serve as indirect measures of disease severity. When used in this way, sample sizes of clinical trials might be reduced, and change in a biomarker or a set of biomarkers could be considered supporting evidence of disease modification. Mass spectrometry-based approaches for protein biomarker discovery and validation offer a new perspective of clinical pathology at the molecular level. In an effort to find biomarkers of Huntington Disease, strategic application of such proteomic approaches to PREDICT-HD samples is proposed. Caprion has already applied these technologies to successfully help develop plasma markers in a patient’s blood for detecting the molecular signature of pulmonary nodules. The Caprion proteomics platform, with integrated and robust processes including sample processing, data acquisition and analysis, biomarker candidate prioritization, assay development and biomarker verification, will be utilized. We propose to find biomarkers using complete clinical assessment information on patients provided by this valuable and unique sample set, in close collaboration and with direction from clinicians, researchers and statisticians from the PREDICT-HD study group.
2018	Wilton	Daniel	Brigham and Women’s Hospital	Application for biosamples from the PREDICT-HD cohort	PREDICT-HD	We find that classical complement cascade proteins are significantly elevated in disease-affected regions of HD mice prior to the appearance of motor and cognitive deficits. Moreover, super resolution microscopy reveals that complement proteins localize to vulnerable cortico-striatal synapses prior to their loss from the striatum. In addition, we have evidence that phagocytic microglia are enriched during the most profound period of synapse loss and engulf more synaptic material. Finally using both genetic and pharmacological tools we have been able to block aspects of this synaptic elimination mechanism and prevent loss of synapses demonstrating the importance of microglia and complement to the development of this pathology. Notably, we find that aspects of this mechanism are also conserved in human disease, as post-mortem tissue reveals evidence of synapse loss, complement deposition at synapses and phagocytic microglia. As a continuation of this work we now wish to assess whether elevated levels of complement proteins can be detected in the CSF of pre-symptomatic HD patients and test the hypothesis that changes in the levels of these proteins will show a positive correlation with clinical aspects of disease progression. In order to address this, we aim to measure levels of complement cascade components and related immune molecules in cerebrospinal fluid (CSF) of HD patients using our validated ELISA assays for C1q, C3, iC3b and C4. To this end we have already carried out some initial analysis on a cohort of samples from the University of Washington in collaboration with Dr Suman Jayadev. Dr Jayadev recruited 8 pre-symptomatic patients in the prodromal phase of the disease as well as 7 controls and carried out parallel clinical

						assessments alongside the collection of CSF and serum samples. This has yielded some encouraging pilot data (see below) and we are now actively seeking CSF from patients at different stages of the disease as well as control (clinically normal) individuals so that we can sufficiently power a study to test the above hypotheses and control for potentially confounding demographic variables such as age and gender. The end goal of this project is to determine if measurements of complement levels in the CSF can predict aspects of disease progression by assessing their correlation with clinical measurements such as the UHDRS TMS. In the process we will also see if complement levels correlate with other known predictors such as CAG length. In addition, testing samples from the PREDICT cohort will provide us with the unique ability to correlate any changes we see in complement CSF levels with data from the bio-imaging studies that have already been carried out. In this way we will be able to see if the observed changes in grey and white matter volume or functional connections occur prior to or following changes in complement levels.
2018	Liu	Jingyu	Mind Research Network	DNA methylation trajectories in prodromal HD	PREDICT-HD	Huntington's disease (HD) is caused by the expansion of a tri-nucleotide CAG repeat within exon 1 of the huntingtin gene. Even though the cause is known, the underlying mechanism of disease progress is far from clear, which leads to variation of age of onset and the severity of symptoms. In this proposal we focus on studying the disease progression during the HD prodromal phase, and focus on the DNA methylation, an epigenetic mechanism regulating gene transcription and expression with converging evidence for its high relevance to HD. Given the fast-emerging knowledge on DNA methylation age (an aggregate measure of multiple CpG sites reflecting the accumulative effect of epigenetic maintenance system) association with ageing-related and neurodegenerative disorders and the well-known glutamate excitotoxicity neuropathology of HD, our investigation targets on DNA methylation age and methylation of glutamate receptor and other HD pathway related genes. We have designed a two-layer association analysis: cross-sectional, and longitudinal. First, we will assess methylation patterns in a cross-sectional sample of prodromal HD, in relation to cognitive, clinical performance, and brain structure. Second, we will assess methylation trajectories in a longitudinal sample of prodromal HD in relation to cognitive, clinical performance, and brain structural changes. By the end of this project, we will determine the consistent hypo- or hyper-methylation changes over time in human prodromal HD, and their clinical relevance in neurodegeneration and progression to diagnosis. As a pilot project of the full proposal, we plan to measure DNA methylation of a preselected 35 genes on 50 samples, with half controls and half prodromal HD participants. The methylation levels of these genes will be compared between prodromal HD and healthy controls and will be tested for associations with cognition and motor scores, and brain structure components.
2018	Wild	Edward	University College London	Neurofilament light protein in cerebrospinal fluid and blood as a prognostic biomarker in premanifest and prodromal Huntington's disease	PREDICT-HD	Neurofilament light protein, an exclusively neuronal protein and component of the axonal cytoskeleton, is increasingly recognised as a valuable biofluid biomarker of neuronal injury and therapeutic response. It is robustly increased in cerebrospinal fluid (CSF) in Huntington's disease (HD) and we recently reported results from the TRACK-HD cohort demonstrating that its level in plasma is prognostic of motor onset, clinical progression and brain atrophy in HD. The present study seeks to extend those findings to determine with considerably greater power and resolution the prognostic potential of NfL in plasma and CSF in premanifest and prodromal HD, both in itself and in comparison to known prognostic factors. This will yield a novel enhanced prognostic index that will be of value for

						clinical trial design, stratification and enrichment, facilitating the advent of biomarker-enhanced trials to prevent the onset of HD.
2020	McGarry	Andrew	Cooper University Hospital at Rowan University	HD-BRAC 2CARE Biosample Application	2CARE	The proposed study is a longitudinal comparison of plasma metabolic changes in HD for fast and slow progressors as defined by functional decline. The rationale for this study is to further investigate findings from a recent cross-sectional pilot metabolomic study we performed in a population representing the entire disease spectrum (HD1 through HD4) (in press, Nat Sci Reports). In those data, concentrations of a number of plasma metabolites correlated to disease severity, including elevations in arginine, citrulline, and glycine, whereas decreases in total serine, D-serine, cholesterol esters, several lipid classes, and sphingomyelins were found. It is unknown whether these observed metabolic findings are consistent across samples from individuals through time or correlate longitudinally with functional progression in a population otherwise clinically and demographically matched at baseline. Further understanding of longitudinal metabolic changes that correlate with functional progression may better identify new disease features (e.g., urea cycle defects) or suggest novel therapeutic approaches (e.g., depletion or repletion of particular metabolites). The 2CARE cohort offers an opportunity to further clarify some of these questions raised by our pilot data. For the proposed study, we will examine plasma metabolite concentrations from 2CARE placebo individuals matched at baseline but with different rates of subsequent progression, using multiple timepoints for each individual across 3-year span.
2023	Osbourn	Jane	Alchemab Therapeutics	B-cell repertoire analysis of HD samples	PREDICT-HD	In this collaboration, Alchemab will apply its technology for deep B-cell repertoire analysis and proteomics in order to improve the understanding of pathophysiological mechanisms of Huntington's disease (HD), investigate the existence of a specific immune signature which contributes to resiliency and may be used as potential therapeutics. Aims of this proposal is to: Aim 1: analyse the B cell receptor (BCR) repertoire Aim 2: analyse the immunoglobulin repertoire interaction profile Aim 3: identify protective, convergent, antigen-associated sequence patterns that may explain the disease progression of HD by using the outcome from the above and deep learning to identify.
2023	Osbourn	Jane	Alchemab Therapeutics	Alchemab MDC collaboration	PREDICT-HD	This access request is a joint venture between Alchemab Therapeutics and Medicines Discovery Catapult (MDC) to further the development of Alchemab's concept for a novel approach to the treatment of Huntington's Disease. The PREDICT HD biofluid samples requested will be used to: • Aim 1: Sera screen patient samples to identify antibodies convergent in resilient individuals. This will enable us to: - o Look for antibodies to Huntingtin protein to identify these individuals and see their corresponding biomarker profile to aid a pre-existing project at Alchemab where a Huntingtin antibody has already been identified - o Discover novel antibodies convergent in resilient HD individuals for additional therapeutic options • Aim 2: Assess various biomarkers at MDC (see project details) to tie in with the identification of any antibodies identified in resilient individuals and to complement a current project at Alchemab where a Huntington antibody has already being identifiedis being developed. It will also complement

						biomarker discovery work which is being done in a R6/1 mouse model treated with Alchemab’s antibody and using the suite of assays available to MDC outlined in the Project details section.
2024	Byrne	Lauren	University College London	Harmonise:HD - Influencing Huntington’s disease monitoring using multi-study integrated analysis of harmonised structural MRI and blood neurofilament light protein.	PREDICT-HD	The Huntington’s Disease Integrated Staging System (HD-ISS) was developed to provide an unambiguous framework for staging Huntington’s disease (HD) mutation carriers from birth to end-stage HD. The inclusion of biological landmarks of pathogenesis (caudate and putamen volume) – which occur years before overt clinical signs and symptoms – could potentially facilitate the design of prevention trials in persons with HD (pwHD) before clinical symptom onset. However, the periods between the earlier HD-ISS (stages 0-2) can span several decades of a pwHD’s lifespan. Additional measures sensitive to the earliest and subtle pathogenic changes could support further stratification and enrichment within HD-ISS 0 and 1, and the potential success of prevention trials. Neurofilament light (NfL) is a biomarker of neuronal damage that has been identified as a promising blood-based biomarker for detecting early pathogenic changes in far-from-onset premanifest pwHD. Characterizing NfL dynamics across the HD-ISS stages will allow the evaluation of its utility for patient enrichment and stratification. Deep understanding of NfL dynamics across the lifespan of individuals with HD is needed to distinguish disease-specific patterns and/or drug-induced changes from natural variations. Frequent remote blood collection studies provide an opportunity to explore the NfL fluctuations over short intervals of time. Together, this will support the interpretation of blood NfL changes in both the clinical trial and disease monitoring settings. This project aims to harmonize blood NfL data from multiple retrospective cohorts, amassing the largest NfL dataset in HD to date. Using this harmonized dataset, we aim to characterize and explore NfL fluctuations across the HD-ISS. We will create a quality short-interval longitudinal NfL dataset using both in-person and remote bi-monthly collected blood samples of pwHD in HD-ISS 0-1 and matched control individuals. The methods and findings from this project will support the development of blood NfL as a biomarker for HD clinical trials and early HD-ISS 0-1 disease monitoring. Future projects will combine harmonized voxel-based morphometry MRI data with this harmonized blood NfL dataset to spatially and temporally map brain morphology changes along NfL trajectories in the lifespan of a pwHD. This will help build evidence as to where NfL in blood is coming from in the brain and uncover specific patterns in HD, further enriching the interpretation of blood NfL in the clinic.
2024	Nopoulos	Peggy	University of Iowa	Somatic Instability in Huntington’s Disease	CHANGE HD, JOHD	We aim to characterize somatic instability in children and young adults with Huntington’s disease (HD), a phenomenon that remains largely unexplored in these age groups. Since the brain cells most affected by HD - particularly those in the cerebral cortex and striatum with pronounced somatic expansion - are not easily accessible, identifying a peripheral biomarker for HTT repeat expansion would be highly valuable for advancing HD research. At the University of Iowa, we currently lack the specialized expertise to measure somatic instability. Therefore, in this study, we will assess somatic instability in a unique population of children and young adults using blood-derived DNA samples (collected from two NIH-funded studies: ChANGE-HD and JOHD), in collaboration with Dr. Darren Monckton at the University of Glasgow, a world-renowned expert in this field.
2025	Southwell	Amber	University of Central Florida	Longitudinal quantification of HTT in circulating brain-derived	PREDICT HD	Current preclinical studies focus on huntingtin (HTT) lowering strategies for Huntington disease (HD). However, its quantification in cerebrospinal fluid (CSF) has been challenging due to the extremely low concentrations and consequent decrease of mutant HTT (mHTT) levels in the CSF after therapy

				extracellular vesicles compared to mHTT in CSF		administration. While a portion of circulating free HTT originates from the brain, it does not correlate with CSF mHTT or symptom severity 8 possibly because it originates from other sources or is modulated by autoantibodies present at varying levels in circulation. Investigation of HTT levels in extracellular vesicles (EVs) originating from the brain and circulating in blood could provide a less-invasive biomarker of brain HTT lowering than CSF mHTT. This would provide a novel peripheral blood biomarker of brain HTT levels. Our initial results demonstrate that neuronal derived vesicles isolated from plasma contain HTT. However, it is unknown if vesicular HTT levels correlate with disease progression. Access to BioSEND samples will allow us to measure and compare HTT levels in neuronal derived EVs in plasma with matched CSF samples. Brain-derived EVs from control and HD patient plasma samples will be isolated using IP and HTT levels will be measured using IP-FCM and compared to CSF mHTT levels and clinical data. This work will contribute to uncovering novel non-invasive clinical biomarkers in liquid biopsies that will allow longitudinal sampling to follow disease progression and evaluate clinical efficacy outcomes.
2025	Paulsen	Jane	University of Wisconsin–Madison	PREDICT-HD	PREDICT HD, PREVENT HD	A partnership among Evotec, the University of Wisconsin biomarker unit and the Paulsen lab will employ immunoassay platforms (i.e., SMCxPRO, MSD, NULISaseq) to measure biofluids obtained during the 12-year Predict study, the 3-year Predict ancillary studies, and the follow-on Prevent study (this request) to provide a biomarker resource for the HD field. The scientific rationale for sample usage at this time is that numerous clinical trials have been completed and are ongoing despite a lack of sufficient biomarkers to guide sample enrollment, document disease progression, monitor treatments, or measure study outcome. Though clinical trials have been successfully completed in HD for over three decades, the need for biomarkers has become prominent with the efforts to enroll persons at earlier stages of disease rendering the traditional enrollment (using persons with a motor diagnosis of HD) and clinical outcome (using the S-F total functional capacity) measures unsuitable. With the development and ongoing improvements of the assays for mHTT in CSF and blood, as well as the multiple additional markers considered relevant for HD, the current grant was funded to examine analytical and clinical validity of biomarkers for very early HD using the Predict cohort of cases across the continuum of HD from Stage 0 to Stage 3 of the HD-ISS.
2025	McGarry	Andrew	Cooper University Healthcare at Rowan University	A longitudinal metabolomic comparison of fast and slow cognitive progression in Huntington's Disease	2CARE	The proposed study is a longitudinal comparison of the plasma metabolome in HD for fast and slow progressors as defined by cognitive decline in 2CARE, a 5-year, randomized, double blind clinical trial. The rationale is to 1) investigate if the fastest and slowest cognitive progressors have different metabolomic signatures and 2) compare fast and slow cognitive progressors to our prior analysis of fast and slow functional progressors, as defined by UHDRS Total Functional Capacity Scores. Differences in metabolomic markers between those with rapid or minimal cognitive decline may reveal candidates for cognitive disability interventions in HD, a disease feature for which no treatment currently exists. Moreover, it is intriguing that the fastest and slowest cognitive progressors in 2CARE are different individuals than the fastest and slowest functional progressors we previously studied, suggesting cognitive decline may have a discrete metabolic profile apart from overall functional status. Evidence continues to accumulate that multiple tissues and organ systems outside of the CNS are affected in HD, including significant dysfunction in processes that may affect the brain (urea cycle,

						glucose metabolism, etc.) and so investigating the peripheral metabolome as reflected in plasma from individuals with differences in cognitive decline is warranted.
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