Review Date	Last Name	First Name	Institution	Title	Cohort	Abstract
2020	Rubel	Carrie	Biogen	READISCA Biosample Access Application	READISCA	Spinocerebellar Ataxia Type 1 (SCA1) and Spinocerebellar Ataxia Type 3 (SCA3) are rare, progressive, invariably fatal monogenic neurodegenerative disorders for which currently no disease-modifying therapies exist. These diseases are caused by a CAG repeat expansion that leads to the formation of a mutant, poly-glutamine (poly-Q) expanded ATXN1 or ATXN3 protein. Mutant poly-Q ATXN1 and ATXN3 proteins cause neuronal damage due to toxic gain-of-function mechanisms. Biochemical biomarkers for SCA1 and SCA3 are not well established. Development of ATXN-specific bioassays are crucial to quantify changes in ATXN protein levels after treatment with potentially disease-modifying treatments that focus on lowering the toxic proteins caused by the repeat expansion. Thus, our key questions are: 1) Can we measure the ATXN1 (or ATXN3) protein in the CSF (and plasma) of SCA1 (or SCA3) patients. 2) If we are able to determine protein levels in these fluid compartments, what is the biological variability in the protein levels in the clinical population? This will be critical for determining the number of subjects that are needed to demonstrate protein lowering. 3) Are there quantifiable biomarkers of neurodegeneration in CSF or plasma that may be relevant to disease progression in SCA1 or SCA3? Our interest is in acquiring READISCA Cerebrospinal Fluid (CSF) and plasma samples to advance fluid biomarker assessments in SCA1 and SCA3. Understanding and characterizing the relevant fluid biomarkers in SCA1 and SCA3 is crucial to inform clinical trial design, evaluation of pharmacodynamic effects and disease progression and, therefore, key to the successful development of potential disease-modifying therapies.
2020	Goyal/Zach	Jaya/Neta	Wave Life Sciences/Takeda	Request for samples for development of mutant ATXN1 and 3 expression assays in CSF and plasma	READISCA	Takeda Pharmaceuticals and Wave Life Sciences, in collaboration, are developing antisense oligonucleotide (ASO) therapies for spinocerebellar ataxia types 1 (SCA 1) and 3 (SCA 3). Development of fluid biomarkers is critical for timely demonstration of pharmacodynamic effects in first-in-human trials, and fluid biomarkers may also yield insights into disease mechanisms and viable therapeutic approaches. However, there is a lack of qualified fluid biomarkers representing underlying pathology for SCA 1 and 3, and the concentrations

						of mutant ataxin in CSF are not known. In this proposal, CSF and plasma samples from READISCA consortium participants with early manifest SCA 1 and SCA 3 will be used to investigate the following fluid biomarker strategies. These assays, if successful, will subsequently be qualified for use as pharmacodynamic biomarkers of ASO therapies for SCA 1 and SCA 3 in first-in human studies.
2021	Opal	Puneet	Northwestern University	Identification of fluid biomarkers in Spinocerebellar ataxia-1	READISCA	Spinocerebellar ataxia-1 (SCA1) is a dominantly inherited neurodegenerative disorder that impacts the cerebellum. Currently, no treatment exists for SCA1. Previous work in preclinical models suggests that ATXN1 lowering strategies targeting RNA (miRNA/ASO/siRNA) improve the disease phenotype. If these strategies are to be translated into therapies for SCA1 patients, it would be important to have assays to detect and monitor the levels of ATXN1; at the same time it would also be helpful to have biomarkers that reflect on disease pathology that can be used in conjunction with clinical rating scales. In this context, we have discovered that the neurofilament light chain (NFL) is an excellent indicator of disease progression in SCA1 mice. Our results are analogous to what has recently been shown with related polyglutamine ataxia SCA3. In this proposal, we will determine assays for NFL and ATXN1 levels in SCA1 patients using their plasma and CSF.
2021	Collins	Abigail	Ionis Pharmaceuticals	Research Strategy for READISCA CSF Samples Ionis Pharmaceuticals	READISCA	SCA1 is a rare dominantly inherited progressive neurodegenerative disorder due to an expanded CAG-triplet repeat mutation in the ATXN1 gene which encodes a protein important for formation and regulation of multimeric nuclear protein complexes. Mutated polyQ Ataxin1 protein has a toxic gain-of-function and ultimately causes pontine and cerebellar degeneration, inexorable progression of ataxia, dysarthria and dysphagia, and death typically within 10-20 years of symptom onset. The biology of Ataxin1 protein in CSF of SCA1 individuals is not understood including whether or how protein levels correlate with symptom onset, disease severity and/or progression over time. Disease-modifying therapies to treat the underlying mechanism of disease in SCA1 will target Ataxin1 protein production and will require demonstration of lowered Ataxin1 levels in CSF as proof of biologic mechanism. Ionis has developed an ATXN1Rx ASO that reduces Ataxin1 mRNA and protein levels in experimental cell lines, healthy

						animals and in a transgenic mouse model of SCA1. Because the amount of protein reduction required for clinical benefit in humans is unknown, it is necessary to be able to reliably measure Ataxin1 concentration in the CSF with varying doses of ATXN1Rx ASO. This information is a crucial component of our clinical trials to enable dose selection, and for interpreting the safety, tolerability and efficacy of this therapeutic approach. Ionis is currently developing an assay to measure Ataxin1 protein levels in human CSF. Ongoing assay development work includes optimization of the testing conditions, and testing Ataxin1 levels in CSF and tissues of animal models treated with the ATXN1Rx ASO. Measuring Ataxin1 protein in CSF of individuals with varying stages of SCA1 is a necessary final step in assay development. This will allow us to advance our ATXN1Rx ASO into clinical trials, a goal of READISCA.
2022	Mohan	Chandra	University of Houston	Circulating protein biomarkers of Spinocerebellar Ataxia	READISCA	Proposed Studies: We propose to ascertain the biomarker potential of 10 selected serum/plasma proteins in SCA, using ELISA assays. A maximum of 6 of these will be drawn from the completed studies: α1-anti-chymotrypsin, GITR, Lipocalin 2 (LCN2), MPO, PGRP-S and proteinase 3. The rest of these 10 candidates will be drawn from the planned 7000-plex proteomic screen. ELISA validation of these 10 proteins will be carried out using serum/plasma obtained from multiple SCA patient cohorts: (A) Cohort I: SCA Patients of Indian origin (PI: Dr. de Silva, Sri Lanka) (B) Cohort II: SCA Patients of Chinese descent (PI: Dr. Wu, China) (C) Cohort III: SCA Patients of Caucasian descent (PIs: Paulson/McLoughlin, USA) (D) READISCA: This cohort is included as it represents the largest, most well documented, multicenter SCA cohort in USA, with good numbers of SCA3 patients with a wide spectrum of SARA and INAS scores.
2023	Sors	Aurore	SERVIER	Request for CSF and plasma samples from SCA2 patients to qualify/validate Ataxin2 expression assays and to	CRC-SCA	To maximize the chances of clinical success, the French pharmaceutical company Servier concentrates its work on genetically validated targets such as Ataxins 2 and 3 in SCA2 and SCA3, and on diseases with target engagement biomarkers. For SCA2 disease, the objective of the Servier

				explore glial and axonal damage biomarkers.		project is to develop an antisense oligonucleotide (ASO) therapy to drive degradation of ATXN2 RNA transcripts via an RNase H mechanism. This should lead to a decrease in Ataxin2 expression to slowdown disease progression in SCA2 patients. In order to assess the target engagement in patients during the clinical trials and so to select the potential therapeutic dose, Servier is currently developing highly sensitive ELISA on the SIMOA® platform to quantify both mutated and normal Ataxin2 in biofluids (CSF and plasma). Servier is requesting CSF and plasma samples from SCA2 patients to qualify/validate Ataxin2 expression assays and to explore some other interesting biomarkers reflecting the glial and axonal damage in this pathology by using commercially available or home-made ELISA. To date, there are very only few publications on axonal damage biomarkers in SCA2, and no data have been published yet on oligodendrocytes (OLs) biomarkers in SCA2. There is a growing interest from the scientific community for OLs involvement in SCA3, this highlights the interest of exploring these biomarkers in biofluids in both SCA3 and SCA2 diseases.
2024	Braas	Daniel	Arrowhead Pharmaceuticals, Inc.	Identifying Potential Biomarkers in SCA2 CSF	CRC-SCA	Arrowhead Pharmaceuticals is developing a novel therapeutic for the treatment for spinocerebellar ataxia type 2 (SCA2). In SCA2 patients, ATXN2 protein is hypothesized to be elevated in CSF as a consequence of disease progression, and thus can be utilized as a biomarker to assess therapeutic target engagement and treatment response. To explore CSF ATXN2 protein as a potential biomarker, we have developed specific and sensitive Ligand Binding Assays (LBAs) based on the Mesoscale Discovery (MSD) Electrochemiluminescence platform and Single Molecule Counting (SMCxPRO) Immunoassay System to quantitate both total ATXN2 protein and ATXN2 with an expanded polyQ region. The SMCxPRO assay has a Lower Limit of Quantitation (LLOQ) than the MSD-based assay and is therefore selected to be further developed. With this application to obtain CSF samples from SCA2 patients, we aim to employ the SMCxPRO assays to assess ATXN2 protein concentration ranges in CSF samples from SCA2 patients. The goal is to evaluate if ATXN2 expression is elevated in CSF from SCA2 individuals and could be exploited as a target-engagement biomarker.