What are biomarkers?
Biomarkers are chemicals that can be measured in the body that can tell us about disease. For example, there are blood tests that can measure cholesterol and sugar that tell us if someone is likely to have heart disease or diabetes. After a medication is given, the test can be repeated to check if the drug is effective. The level of the biomarker can also tell us about the severity of the disease in the patient.

Why are biomarkers urgently needed for INAD?
For INAD, there are currently no biomarkers. This could potentially hamper the development of effective therapies for INAD because with any proposed treatment, it will be harder to measure how effective it is.

Potential benefits of developing a biomarker for INAD

- To help doctors make the diagnosis earlier in patients
- To improve our understanding of disease
- To provide a more accurate picture to families of what the future holds for their child (prognosis)
- To assess how severe the disease is and how quickly it is progressing
- To help assess the effectiveness of upcoming new treatments in clinical trials

What progress has been made?
In 2022, Cure INAD UK provided University College London (UCL) / Great Ormond Street Children's Hospital team £7222 for INAD research. This funding was used to fund research into developing biomarkers for INAD (also called *PLA2G6*-associated Neurodegeneration or PLAN).

Progress has been excellent. Although this is an ultra-rare disorder, thanks to the contributions of the INAD/PLAN international community, a large number of patient samples have been collected including:

- **Blood:** 60 PLAN samples, 14 control or healthy children samples
- **Urine:** 38 PLAN samples, 13 control or healthy children samples
- **Cerebrospinal fluid (CSF)*:** 8 PLAN samples, 13 healthy children samples

**CSF is fluid from around the brain and spinal cord. This fluid can be obtained through a lumbar puncture procedure where a needle is placed into the back to collect the fluid. These samples were not taken specifically for this research project, rather they are samples that were obtained and stored previously by their local doctors, prior to making the diagnosis of PLAN.*

Several provisional INAD biomarkers that have the potential to tell us about disease progression have been identified in patient blood and CSF on our early analysis. Ongoing work is being performed to validate and confirm these promising findings.

Alongside the biomarker work, the UCL team are also:
1. Completing a large international history study of almost 300 patients to try and understand the natural course of disease in PLAN – this work will help us understand whether any new therapies make a difference to the natural course of disease.

2. Validating a new disease-specific clinical rating scale that will help us to objectively determine the stage of disease for any given patient
3. Quantifying the brain changes seen on brain MRI scans of children with INAD.

We have also secured further funding from Bloomsbury Genetic Therapies to continue this work. We hope to have a publication in a peer-reviewed, scientific journal by the end of 2023. Our multimodal approach of measuring disease progression will help the INAD community to be trial-ready for future clinical studies, such as the gene therapy that is being developed by UCL and Bloomsbury Genetic Therapies, now in an advanced stage of preclinical development.