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| **Familial Disease Cohorts**  Work Package 5 |
| **Objective(s)**: |
| To establish a familial disease (inherited) cohort drawn from the UCL FAD (including DIAN), Familial FTD (including GENFI), HD (Track HD) and new LRKK2 cohorts to provide unique biomarker validation identifying disease specific and disease common biomarkers.  More specifically to:   1. Familial cohorts not currently associated with DPUK will be scoped to clarify opportunities for synergy between familial and population-based cohorts. 2. Comparison of familial case (HD, FAD, FTD, LRRK2) close to symptom onset and with premanifest evidence of atrophy, to assess proteomic profiles that may be common to all four diseases. It was proposed to link this work to WP6 and for it to be used as an early study to establish the processes allowing access to the wider bioresources associated with these multi-national studies. 3. Comparison of premanifest tau mutation carriers using AV1451 together with csf A13 and tau. 4. Aid recruitment to the nascent LRRK cohort 5. Validation studies of biomarkers identified in population cohort in WP3 (UK Biobank) and WP4 (1946 birth cohort) |
| **Overview Summary:** |
| At UCL the team has been working with small groups of individuals with rare familial (inherited) forms of dementia. Focusing on familial Alzheimer’s disease (FAD), familial frontotemporal dementia (FTD), Huntington’s Disease (HD) and a new cohort of familial Parkinson’s Disease where individuals have a LRKK2 gene mutation, the aim was to achieve a detailed understanding of disease progression from the presymptomatic stage to established disease. One focus was on biomarkers to enable diagnosis and disease progress monitoring. This work would link with other DPUK work packages (WP3, WP4 and WP6).  The work demonstrated that PET imaging had limited use in FTD but that studying neuroinflammation may be more informative. In addition, the studies shown accelerated forgetting was an additional marker for FAD, with this test now being considered for inclusion in a major international study. Serum Neurofilament light (NfL) was also demonstrated to be a robust measure of neurodegeneration in AD, FTD and HD. |
| **Executive Summary:** |
| The project aimed to create, or expand, cohorts of familial (inherited) dementias including Alzheimer’s disease (AD), frontotemporal degeneration (FTD), Huntington’s Disease (HD) and Parkinson’s Disease (PD). Autosomal dominant degenerative dementias are highly penetrant with similar ages at onset within families. This provides the opportunity to study mutation carrying individuals from premanifest to established disease. Non mutation carrier siblings are ideal controls due to shared genetics (other than mutation) and early environment.  The project team built on extant cohorts of familial Alzheimer’s disease (FAD), familial frontotemporal dementia and Huntington’s Disease and developed a new cohort of familial Parkinson’s Disease with a LRKK2 gene mutation. Importantly, the project linked with international studies such as DIAN, GENFI and Track HD. The work aimed to achieve a detailed understanding of the individual diseases from the very first presymptomatic manifestations through to established disease and biomarkers to enable diagnosis and monitoring of progression.  The team has been productive and publications describing a variety of longitudinal measures are detailed below. Most of the work was undertaken as planned, with the addition of a programme to evaluate serum neurofilament light (NfL). The team demonstrated that NfL was an early biomarker of disease progression in FAD and in collaboration with WP4, that it behaved similarly in sporadic disease. The work demonstrated that the NfL results were not disease specific but reflected neurodegeneration in HD and FTD as well.  Specific results obtained, and currently being written up for publication, have shown that in familial FTD, PET imaging has limited application and study of neuroinflammation, as measured by microglial activation *in vivo,* is more informative. Additional funding identified accelerated forgetting as a novel marker of cognitive decline in FAD and this test is now been considered for inclusion in a major international study.  The team has also been major contributors to GENFI, the international multicentre cohort study investigating genetic forms of FTD.  A major focus of GENFI is now the development of biomarkers and batteries of tests with further work on trials of novel therapies planned in conjunction with pharma companies. |
| **Summary of Outputs**: (as per Researchfish categories) |
| **Publications:** |
| * Weston, P.S.J., Poole, T., Nicholas, J.M. et al. **Measuring cortical mean diffusivity to assess early microstructural cortical change in presymptomatic familial Alzheimer’s disease**. *Alz Res Therapy* 12, 112 (2020). [doi.org/10.1186/s13195-020-00679-2](https://doi.org/10.1186/s13195-020-00679-2)   *There is increasing interest in improving understanding of the timing and nature of early neurodegeneration in Alzheimer’s disease (AD) and developing methods to measure this in vivo. Autosomal dominant familial Alzheimer’s disease (FAD) provides the opportunity for investigation of presymptomatic change. Cortical MD measurement detects microstructural breakdown in presymptomatic FAD and correlates with proximity to symptom onset independently of cortical thickness. Cortical MD may thus be a feasible biomarker of early AD-related neurodegeneration, offering additional/complementary information to conventional MRI measures.*   * O’Connor, A., Karikari, T.K., Poole, T. et al. **Plasma phospho-tau181 in presymptomatic and symptomatic familial Alzheimer’s disease: a longitudinal cohort study**. *Mol Psychiatry* (2020). [doi.org/10.1038/s41380-020-0838-x](https://doi.org/10.1038/s41380-020-0838-x)   *Blood biomarkers have great potential to advance clinical care and accelerate trials in Alzheimer’s disease (AD). Plasma phospho-tau181 (p-tau181) is a promising blood biomarker however, it is unknown if levels increase in presymptomatic AD. We examined the relationship between p-tau181 and neurofilament light and estimated years to/from symptom onset (EYO), as well as years to/from actual onset in a symptomatic subgroup. In addition, we studied associations between p-tau181 and clinical severity, as well testing for differences between genetic subgroups. Our finding that plasma p-tau181 concentration is increased in symptomatic and presymptomatic FAD suggests potential utility as an easily accessible biomarker of AD pathology.*   * Franzmeier N, Koutsouleris N, Benzinger T, et al. **Predicting sporadic Alzheimer's disease progression via inherited Alzheimer's disease-informed machine-learning**. *Alzheimers Dement*. 2020;16(3):501-511. <doi:10.1002/alz.12032>   *Developing cross‐validated multi‐biomarker models for the prediction of the rate of cognitive decline in Alzheimer's disease (AD) is a critical yet unmet clinical challenge. We applied support vector regression to AD biomarkers derived from cerebrospinal fluid, structural magnetic resonance imaging (MRI), amyloid‐PET and fluorodeoxyglucose positron‐emission tomography (FDG‐PET) to predict rates of cognitive decline. Our independently validated machine‐learning model predicted cognitive decline in sporadic prodromal AD and may substantially reduce sample size needed in clinical trials in AD.*   * Convery RS, et al. **Longitudinal (18F)AV-1451 PET imaging in a patient with frontotemporal dementia due to a Q351R MAPT mutation.** J Neurol Neurosurg Psychiatry. 2019 Aug 22. [Epub ahead of print]   *Mutations in the microtubule associated protein tau (MAPT) gene are a common cause of inherited frontotemporal dementia (FTD) and result in the deposition of pathological tau protein in the brain. Here we describe longitudinal (18F)AV-1451 PET imaging from a patient with FTD due to a Q351R mutation located on exon 12 of the MAPT gene.6*   * Vöglein J., et al (2019). **Seizures as an early symptom of autosomal dominant Alzheimer's disease.** *Neurobiology of Aging*, *76*, 18-23. doi:10.1016/j.neurobiolaging.2018.11.022   *This paper assessed the reported history of seizures in cognitively asymptomatic mutation carriers for* [*autosomal dominant*](https://www.sciencedirect.com/topics/medicine-and-dentistry/autosomal-dominant-inheritance)[*Alzheimer's disease*](https://www.sciencedirect.com/topics/medicine-and-dentistry/alzheimers-disease) *(ADAD) and the predictive value of seizures for mutation carrier status in cognitively asymptomatic first-degree relatives of ADAD patients. Among cognitively asymptomatic ADAD family members, the occurrence of seizures increases the a priori risk of 50% mutation-positive status to about 80%. This finding suggests that ADAD mutations increase the risk of seizures*.   * Franzmeier, N., et al. (2019). **The BDNFVal66Met SNP modulates the association between beta-amyloid and hippocampal disconnection in Alzheimer's disease**. *Mol Psychiatry*. doi:[10.1038/s41380-019-0404-6](http://doi.org/10.1038/s41380-019-0404-6)   *This study suggests that BDNFVal66Met is selectively associated with a higher vulnerability of hippocampus-frontal connectivity to primary AD pathology, resulting in greater AD-related cognitive impairment. The effect of BDNFVal66Met on functional networks that may underlie cognitive impairment in AD is poorly understood. Using a cross-validation approach, we first explored in subjects with autosomal dominant AD (ADAD) from the Dominantly Inherited Alzheimer Network (DIAN) the effect of BDNFVal66Met on resting-state fMRI assessed functional networks*.   * Vöglein, J et al. **Clinical, pathophysiological and genetic features of motor symptoms in autosomal dominant Alzheimer’s disease,** *Brain*, awz050. [doi.org/10.1093/brain/awz050](https://doi.org/10.1093/brain/awz050)   *This study assessed the prevalence and characteristics of motor signs in autosomal dominant Alzheimer’s disease. Motor symptoms were explored with respect to associations with mutation carrier status, mutation site within PSEN1, basal ganglia amyloid-8 as measured by Pittsburgh compound B PET, estimated years to symptom onset and Clinical Dementia Rating Scale-Sum of Boxes. With a prevalence of approximately 30% and increasing severity with progression of dementia, motor symptoms are proven as a clinically relevant finding in autosomal dominant Alzheimer’s disease, in particular in advanced dementia stages that correlates with deposition of amyloid-8 in the basal ganglia*.   * Preische, O et al. (2019) **Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer’s disease.** Nature Medicine. 2019 Jan 31; 25:277-283. doi: 10.1038/s41591-018-0304-3   *Validates the initial observations that Neurofilament light chain (NfL) is a promising fluid biomarker for disease progression for various cerebral proteopathies. Using the DIAN cohort and an ultrasensitive immunoassay demonstrates that NfL in CSF and serum are elevated in the presymptomatic stages of familial AD. The rate of change in serum NfL is more informative than cross-sectional absolute NfL levels, detecting changes in a timeline of 16.2 years versus 6.8 years before symptom onset. The increased rate of change in NfL was strongly associated with cortical thinning measurements determined by MRI but less with amyloid-8-deposition or glucose metabolism via PET. Overall, this important paper demonstrates that NfL dynamics in serum predict disease progression and neurodegeneration at the early presymptomatic stages of familial AD and is a potentially useful biomarker*.   * Müller, S., et al. **Dominantly Inherited Alzheimer Network (DIAN). (2018). Relationship between physical activity, cognition, and Alzheimer pathology in autosomal dominant Alzheimer's disease.** Alzheimers Dement. doi:10.1016/j.jalz.2018.06.3059   *Little is known about effects of physical activity (PA) in genetically driven early-onset autosomal dominant Alzheimer's disease (AD). A total of 372 individuals participating at the Dominantly Inherited Alzheimer Network study were examined to evaluate the cross-sectional relationship of PA with cognitive performance, functional status, cognitive decline, and AD biomarkers in cerebrospinal fluid. Mutation carriers were categorized as high or low exercisers according to WHO recommendations. Mutation carriers with high PA showed significantly better cognitive and functional performance and significantly less AD-like pathology in cerebrospinal fluid than individuals with low PA. Mutation carriers with high PA scored 3.4 points better on Mini Mental State Examination at expected symptom onset and fulfilled the diagnosis of very mild dementia 15.1 years later compared with low exercisers. These results support a beneficial effect of PA on cognition and AD pathology even in individuals with genetically driven autosomal dominant AD.*   * Ángel Araque Caballero, M., et al. (2018). **White matter diffusion alterations precede symptom onset in autosomal dominant Alzheimer’s disease.** Brain. doi:10.1093/brain/awy229   *Here, we assessed mean diffusivity alterations in the white matter in 64 mutation carriers compared to 45 non-carrier family non-carriers. Using tract-based spatial statistics, we mapped the interaction of mutation status by estimated years from symptom onset on mean diffusivity. The earliest increase of mean diffusivity was observed in the forceps major, forceps minor and long projecting fibres-many connecting default mode network regions-between 5 to 10 years before estimated symptom onset. Higher mean diffusivity in fibre tracts was associated with lower grey matter volume in the tracts' projection zones. Results suggest that regionally selective white matter degeneration occurs years before the estimated symptom onset. Such white matter alterations are associated with primary Alzheimer's disease pathology and microglia activity in the brain.*   * McDade, E., et al. **Dominantly Inherited Alzheimer Network. (2018). Longitudinal cognitive and biomarker changes in dominantly inherited Alzheimer disease.** Neurology. doi:10.1212/WNL.0000000000006277   *To assess the onset, sequence, and rate of progression of comprehensive biomarker and clinical measures across the spectrum of Alzheimer disease (AD) using the Dominantly Inherited Alzheimer Network (DIAN) study and compare these to cross-sectional estimates. We conducted longitudinal clinical, cognitive, CSF, and neuroimaging assessments (mean of 2.7 [±1.1] visits) in 217 DIAN participants. Linear mixed effects models were used to assess changes in each measure relative to individuals' estimated years to symptom onset and to compare mutation carriers and noncarriers. Longitudinal 8-amyloid measures changed first (starting 25 years before estimated symptom onset), followed by declines in measures of cortical metabolism (approximately 7-10 years later), then cognition and hippocampal atrophy (approximately 20 years later). There were significant differences in the estimates of CSF p-tau181 and tau, with elevations from cross-sectional estimates preceding longitudinal estimates by over 10 years; further, longitudinal estimates identified a significant decline in CSF p-tau181 near symptom onset as opposed to continued elevations. These longitudinal estimates clarify the sequence and temporal dynamics of presymptomatic pathologic changes in autosomal dominant AD, information critical to a better understanding of the disease. The pattern of biomarker changes identified here also suggests that once 8-amyloidosis begins, additional pathologies may begin to develop less than 10 years later, but more than 15 years before symptom onset, an important consideration for interventions meant to alter the disease course.*   * Franzmeier, N., et al. (2018). **Left frontal hub connectivity delays cognitive impairment in autosomal-dominant and sporadic Alzheimer's disease.** Brain: a journal of neurology. doi:10.1093/brain/awy008   *Patients with Alzheimer's disease vary in their ability to sustain cognitive abilities in the presence of brain pathology. Higher functional MRI-assessed functional connectivity of a hub in the left frontal cortex is a core candidate brain mechanism underlying reserve as it is associated with education (i.e. a protective factor often associated with higher reserve) and attenuated cognitive impairment in prodromal Alzheimer's disease. However, no study has yet assessed whether such hub connectivity of the left frontal cortex supports reserve throughout the evolution of pathological brain changes in Alzheimer's disease, including the presymptomatic stage when cognitive decline is subtle. Our findings suggest that higher resilience against the development of cognitive impairment throughout the early stages of Alzheimer's disease is at least partially attributable to higher left frontal cortex-hub connectivity*.   * [Scott CJ., et al. (2018).](https://app.researchfish.com/portfolio/0/publications/5c7541fd5219b6.78037161/view?name=5c7541fd5219b6.78037161&delegator=39791&filter=MRC--MR/L023784/2) **Reduced acquisition time PET pharmacokinetic modelling using simultaneous ASL-MRI: proof of concept.** Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism, pp. 271678X18797343 * [Woollacott I., et al. (2018).](https://app.researchfish.com/portfolio/0/publications/5c644fdeb2dda3.63500015/view?name=5c644fdeb2dda3.63500015&delegator=39791&filter=MRC--MR/L023784/2) **Pathological correlates of white matter hyperintensities in a case of progranulin mutation associated frontotemporal dementia.** Neurocase, 24 (3), pp. 166-174 * [Gordon B., et al. (2018).](https://app.researchfish.com/portfolio/0/publications/5c644a44e6a0e7.58215233/view?name=5c644a44e6a0e7.58215233&delegator=39791&filter=MRC--MR/L023784/2) **Spatial patterns of neuroimaging biomarker change in individuals from families with autosomal dominant Alzheimer's disease: a longitudinal study.** The Lancet Neurology, * [Weston PSJ., et al. (2018).](https://app.researchfish.com/portfolio/0/publications/5aa92e0166dc30.08596693/view?name=5aa92e0166dc30.08596693&delegator=39791&filter=MRC--MR/L023784/2) **Accelerated long-term forgetting in presymptomatic autosomal dominant Alzheimer's disease: a cross-sectional study.** The Lancet. Neurology, 17 (2), pp. 123-132 * [Schott JM., et al. (2016).](https://app.researchfish.com/portfolio/0/publications/5a9fb87f0aaf08.66735452/view?name=5a9fb87f0aaf08.66735452&delegator=39791&filter=MRC--MR/L023784/2) **Inflammatory changes in very early Alzheimer's disease: friend, foe, or don't know?** Brain: a journal of neurology, 139 (Pt 3), pp. 647-50 * [Brown BM., et al. (2017).](https://app.researchfish.com/portfolio/0/publications/5a6f325d934a92.92794676/view?name=5a6f325d934a92.92794676&delegator=39791&filter=MRC--MR/L023784/2) **Habitual exercise levels are associated with cerebral amyloid load in presymptomatic autosomal dominant Alzheimer's disease.** Alzheimer's & dementia: the journal of the Alzheimer's Association, 13 (11), pp. 1197-1206 * [Kinnunen KM., et al. (2018).](https://app.researchfish.com/portfolio/0/publications/5a098b7b42b2a1.41860115/view?name=5a098b7b42b2a1.41860115&delegator=39791&filter=MRC--MR/L023784/2) **Presymptomatic atrophy in autosomal dominant Alzheimer's disease: A serial magnetic resonance imaging study.** Alzheimer's & dementia: the journal of the Alzheimer's Association, 14 (1), pp. 43-53 * [Weston PSJ., et al. (2017).](https://app.researchfish.com/portfolio/0/publications/5a098b79f29d63.81958134/view?name=5a098b79f29d63.81958134&delegator=39791&filter=MRC--MR/L023784/2) **Serum neurofilament light in familial Alzheimer disease: A marker of early neurodegeneration.** Neurology, 89 (21), pp. 2167-2175 * [Ritchie CW., et al. (2017). T](https://app.researchfish.com/portfolio/0/publications/5a098b7a21cfb4.49036418/view?name=5a098b7a21cfb4.49036418&delegator=39791&filter=MRC--MR/L023784/2)**he Edinburgh Consensus: preparing for the advent of disease-modifying therapies for Alzheimer's disease.** Alzheimer's research & therapy, 9 (1), pp. 85 * [Lim YY., et al. (2016).](https://app.researchfish.com/portfolio/0/publications/58c7d46dbd7267.70846795/view?name=58c7d46dbd7267.70846795&delegator=39791&filter=MRC--MR/L023784/2) **BDNF Val66Met moderates memory impairment, hippocampal function and tau in preclinical autosomal dominant Alzheimer's disease.** Brain: a journal of neurology, 139 (Pt 10), pp. 2766-2777 * [Weston PS., et al. (2016).](https://app.researchfish.com/portfolio/0/publications/58a44b38dea301.46553282/view?name=58a44b38dea301.46553282&delegator=39791&filter=MRC--MR/L023784/2) **Presymptomatic cortical thinning in familial Alzheimer disease: A longitudinal MRI study.** Neurology, 87 (19), pp. 2050-2057 * [Ryan NS., et al. (2016).](https://app.researchfish.com/portfolio/0/publications/5832c5467c1bd6.02664390/view?name=5832c5467c1bd6.02664390&delegator=39791&filter=MRC--MR/L023784/2) **Clinical phenotype and genetic associations in autosomal dominant familial Alzheimer's disease: a case series.** The Lancet. Neurology, 15 (13), pp. 1326-1335 * [Tang M., et al. (2016).](https://app.researchfish.com/portfolio/0/publications/5832c5469b4f62.69972074/view?name=5832c5469b4f62.69972074&delegator=39791&filter=MRC--MR/L023784/2) **Neurological manifestations of autosomal dominant familial Alzheimer's disease: a comparison of the published literature with the**   [**Dominantly Inherited Alzheimer Network observational study (DIAN-OBS).**](https://app.researchfish.com/portfolio/0/publications/5832c5469b4f62.69972074/view?name=5832c5469b4f62.69972074&delegator=39791&filter=MRC--MR/L023784/2) The Lancet. Neurology, 15 (13), pp. 1317-1325 |
| **Collaborations & Partnerships** |
| The nature of this work on patients with rare familial forms of dementia necessitates a collaborative effort in order to study sufficient individuals to provide robust scientific findings. The study proposed intended to build on collaboration with DPUK researchers undertaking work in other workpackages (WP3, WP4 and WP6). In addition, the team have been major contributors to GENFI, the international multicentre cohort study investigating genetic forms of FTD. The team has also been involved in DIAN. |
| **Further Funding** |
| The DPUK award was supplemented by other funding enabling the study to be more comprehensive and have a broader scope. |
| **Next Destinations** |
| This project has been the research focus for 13 PhD students who have either completed or are completing their research studies. |
| **Engagement Activities** |
| **2020**   * Fox N - “Early onset AD” Plenary- Alzheimer’s Association International Conference - Amsterdam-virtual (July 2020) * Rossor M. - Interview European Brain Council (March 2020) * Fox N - “Insights from imaging of familial AD” AD/PD Vienna virtual (March 2020) * Fox N. - Biomarkers of presymptomatic Alzheimer’s disease. Munster neuroscience meeting, Cork University Hospital (February 24th 2020) * Fox N - “Familial AD Insights: aetiology, heterogeneity and presymptomatic change” (ICM (plenary) –Paris Jan 2020) **2019** * Rossor M. - NIHR Podcast Series interview (December 2019) * Rohrer J - NISALS 2019: 10 years of FTD imaging and the decade ahead (Oxford, October 2019) * Fox N. - ‘The sequence and timing of preclinical cognitive decline in Autosomal dominant Alzheimer’s disease.’ O’Connor A, Oxtoby N, Weston P, Pavisic I, Ryan N, Lu K, Crutch S, Alexander D, Fox N. 55th Annual Meeting of the Irish Neurological Association (INA), Cork (June 2019) * Fox N - Longitudinal F-AV-1451 Tau PET in familial Alzheimer’s disease. O’Connor A, Markiewicz, Cash D, Scholl M, Weston P, Ryan N, Pavisic I, Lu K, Fraser M, Malone I, Fox N. Alzheimer’s Association International Conference (AAIC), Los Angeles (July 2019) * Fox N - The sequence and timing of preclinical cognitive decline in Autosomal dominant Alzheimer’s disease. O’Connor A, Oxtoby N, Weston P, Pavisic I, Ryan N, Lu K, Crutch S, Alexander D, Fox N. Alzheimer’s Association International Conference (AAIC), Los Angeles (July 2019) * Rohrer J - Swedish FTD Initiative: Genetic FTD – the story so far (Stockholm, March 2019) * Fox N - “Prevention of Dementia: Trials – Opportunities & Challenges” Key note - International Alzheimer’s Disease Conference (Hong Kong 2019)   **2018**   * Fox N. - Co-chair for a session at an ARUK workshop: tackling gaps in Developing Life-Changing Treatments for Dementia 2018 * Fox N - ABN – 2018 - Longitudinal measurement of serum neurofilament light concentration in familial Alzheimer’s disease - Phil Weston * Fox N - AAIC 2018 - “Accelerated long-term forgetting in familial Alzheimer’s disease” - Phil Weston * Rohrer J - Erasmus FTD Seminar: Neuroimaging of FTD (Rotterdam, November 2018)   **2017**   * Fox N - The Guardian - Terry Jones: I've got dementia. My frontal lobe has absconded * Rossor M. - Joint Programme for Neurodegenerative Disease (JPND) Scientific Advisory Board (SAB) strategic workshop on precision medicine (13 March 2017) * Rossor M. - European Brain Council Strategic Workshop (13 and 14 September 2017) * Rossor M. - Dementia and Neurodegeneration Network Ireland (DNNI) Inaugural conference (30 November 2017) * Fox N - “Heterogeneity and familial (autosomal dominant) Alzheimer’s disease” (AAIC 2017) * Rohrer J - ADPD 2017 Developing biomarkers for FTD (Vienna, April 2017)   **2016**   * Rossor M. - British NeuroPsychiatric Association Annual meeting 24th February - medalist Lecture 2016, 2017 * Rossor M. - 6-7 April 2016, DZNE (Bonn)"The role of genetic cohorts in bridging clinical and basic science" * Rossor M. - 26 April 2016, DPUK Annual Conference * Rossor M. - 5-7 October 2016, CCNA ISAB (Vancouver) (premanifest disease & cognitive footprint?) * Rossor M. - November 2016, WISH Summit (Qatar) * Fox N. - “Data-driven models of biomarker changes in Alzheimer’s disease.”Neil Oxtoby, Alexandra Young, Daniel Alexander. ADNI Private Partners Scientific Board Meeting, Washington DC, USA, December 2016. * Fox N - Longitudinal Atrophy in Autosomal Dominant AD - David M Cash; Kirsi M. Kinnunen; Philip SJ Weston; Natalie S Ryan; Marc Modat; Randall Bateman; John C. Morris; Sebastien Ourselin; Martin N Rossor; Tammie L. S. Benzinger; Nick C Fox; and DIAN (AAIC 2016) * Fox N - “What have we learned and what can we expect from imaging in AD” Plenary - CTAD (San Diego 2016)   **2015**  Fox N. - Dementia and a Research Institute - Interview in the Sun Newspaper 5 Oct 15 |
| **Influence of policy, practice, patients & the public** |
| Serum neurofilament light has been established as a robust biomarker of neurodegeneration that is now being included as an outcome measure in clinical trials. |
| **Research Tools & Methods** |
| The team has been responsible for development of a rich variety of cognitive, imaging and molecular markers (see publications). |
| **Research Databases & Models** |
| Cohort data from GENFI and Track HD are now available via DPUK. |
| **Intellectual property & licencing** |
| None |
| **Medical products, interventions & clinical trials** |
| None |
| **Artistic & creative products** |
| None |
| **Software & technical products** |
| None |
| **Spin outs** |
| None |
| **Awards & recognition** |
| None |
| **Other outputs & knowledge/future steps** |
| None |
| **Use of facilities & resources** |
| Data from the project has been deposited on the DPUK Data portal. |
| **Most successful outcome and what it means for future dementia research**: |
| The team has added to the value of using autosomal dominantly inherited degenerative dementias to map out the natural history of the disease from pre-manifest through to established disease. As part of major international collaborations of DIAN and GENFI, a rich variety of cognitive, imaging and molecular markers have been detailed. Serum NfL has been shown to be a robust marker of neurodegeneration *per se* that is being incorporated into clinical trials as an outcome measure. |
| **Lessons learned**: |
| The main lesson has been the value of using autosomal dominantly inherited genetic forms of neurodegenerative dementias to map out the national history of the disease from pre-manifest through to established disease and, therefore, identify early manifestations. This reflects a long history of research, particularly into familial Alzheimer’s disease taking place at UCL. |
| **Other:** |
| Report finalised on 10 November 2020. |