MRC-NIHR Rare Disease Research Platform: Nodes

List of applications invited to the full stage, with abstracts from the outline stage (outline panel meeting held 08 December 2022). *[List updated 26 January 2023]*

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1 Rare disease and mental health - a cross-cutting node

Lead applicant: **Dr Kate Baker, University of Cambridge**

Abstract: There are around 8000 different rare diseases, together affecting 1 in 17 people. Compared to people without a rare disease, people with a rare disease are more likely to experience mental health difficulties, such as depression and anxiety. Mental health symptoms are distressing, and disruptive to relationships, employment and social life. They can also prevent access to specialist treatments and participation in research. Over time, mental health problems can be as debilitating as the rare disease itself. Parents/carers of people with rare disease are also vulnerable to mental health difficulties, magnifying the impact of rare disease on families.

In order to proactively target support and effectively treat symptoms, we need to know which rare disease patients and families are at highest risk, when risk is highest, and why mental health difficulties sometimes persist. However, current research about mental health in rare diseases tends to focus on specific rare conditions or single risk factors, and is not joined-up, thus having limited benefit. The Rare Disease and Mental Health Node will bring about a step-change by creating a new national network of patient groups, medical professionals and researchers to tackle this major challenge together. The node aims to find out which factors increase or reduce mental health risk across all rare diseases, a first step toward changing how mental health is supported.

There are many contrasting factors which influence mental health amongst rare disease patients and their family members. Some rare conditions affect brain function directly, making mental health symptoms more likely. Other rare conditions mainly affect physical health, with knock-on emotional consequences. Patients often experience many years of symptoms and medical tests before a diagnosis is reached, entailing prolonged stress with enduring mental health effects. Any long term or serious health problem can prompt uncertainties and lifestyle changes, but a rare diagnosis can be additionally isolating because of limited information, lack of professional expertise, and lack of contact with others sharing the same condition. Living with a rare disease can lead to financial hardship, compounding mental health risks. Whilst some of these risk factors are unavoidable, it is important to understand how they combine and lead to long-term mental health problems for some (but not all) patients and their families.

Our first activity will be co-production of the node's priorities, working together with rare disease patients and family members including those who have experienced mental health difficulties. The node will then meet annually to shape activities and review progress. Network sub-teams will lead workshops on specific topics, such as mental health in rare intellectual disability syndromes, and mental health of parents and siblings. We will hold two residential events for node members and rare disease platform representatives, to integrate information about specific rare diseases into mental health activities, and feedback our results into other rare disease research. Three short-term projects will be carried out. These will (1) analyse existing rare disease/mental health data in a combined and co-ordinated way, (2) identify where combinations of rare disease and mental health information exist in routine healthcare data and (3) develop effective ways to study parent/carer mental health before and after genetic testing.

The outcomes from this node will pave the way for future larger scale research with direct clinical benefits across the rare disease population. The network will produce evidence-based articles summarising the existing knowledge, identifying research gaps, making recommendations for future research, and suggestions for clinical practice. We will also produce a mental health toolkit for rare disease researchers, and train the next generation of rare disease mental health research leaders.

2 Establishing an integrated rare genetic skeletal disorders (GSD) research node: from genomics to therapeutic targets and stratified medicine

Lead applicant: **Dr Meena Balasubramanian, University of Sheffield**

Abstract: Rare diseases are often complex, require multi-disciplinary management and often go unrecognised outside specialist settings. This is especially true of metabolic bone disorders and skeletal dysplasias collectively referred to as GSDs which are individually rare. Early diagnosis is important to ensure appropriate initiation of management and avoidance of the 'diagnostic odyssey' that many of these families experience. However, beyond early diagnosis, there are no specific guidelines on management and interventions (both surgical and non-surgical) for these conditions making it highly important to establish a GSD translational node focused on a continuum from diagnosis, management to discovery of new therapeutics for these disorders.

Genetic skeletal disorders (GSDs) comprise >450 unique phenotypes that affect a broad range of connective tissues including cartilage and bone. GSDs are archetypal examples of rare diseases that are chronically debilitating, often life-threatening and for which no treatments are currently available for the majority of sub-types. There has been a lot of recent interest in GSDs due to shared biological pathways between GSDs and common diseases of ageing, such as Osteoarthritis and Osteoporosis which are becoming increasingly prevalent with an ageing population.

In addition, in the basic science space, GSDs and study of these conditions play a key role in understanding common disease mechanisms and emphasis on tissue regeneration. Over the last decade, there has been an increase in innovation and investment in therapeutics for GSDs.

Developing new treatments for rare diseases has become increasingly common with a number of high cost therapies now NICE-approved and funded for GSDs, eg: asfotase alfa (recombinant human alkaline phosphatase) for hypophosphatasia; and burosumab (monoclonal anti-FGF23 antibody) for X-linked hypophosphatemia. Other targeted treatments are in phase III stage for OI (setrusumab) and achondroplasia (vosoritide; infragratinib). Such treatments have revolutionised patient outcomes. Mechanistic insights benefit patients, but also provide wider benefit; for example, the study of rare childhood-onset bone diseases (osteoporosis-pseudoglioma syndrome; sclerosteosis) underpinned development of two new osteoporosis treatments (anti-RANK-ligand antibody- denosumab; anti-sclerostin antibodies- romosumab, setrusmab). Thus, uncovering new knowledge about rare genetic disorders will lead to potentially new drug targets for a wide range of human disorders.

The focus of this UKRI Rare Disease Research Platform is to develop a GSD node based in Sheffield with a network of specialist centres across the whole of the UK including 5 centres in England and atleast 3 further centres in each of the devolved nations. This will enable seamless translation of GSD research from early diagnosis, phenotyping and preparing trial-ready cohorts of GSD patients to enable early industry engagement and establishing natural history studies focused on specific GSDs as part of this application.

The GSD node will address several research challenges including lack of standardised diagnostic and therapeutic approaches across the spectrum of GSDs due to lack of knowledge of specific disorders and small individual cohort sizes. The systematic capture and follow-up of GSD cohorts will also allow them to become trial-ready when new opportunities arise and will help to create new models of integrated follow-up. A second challenge is the gap between potentially available novel therapy modalities and when it actually reaches a patient with GSD as timely intervention during growth is critical for improved outcomes. By combining efforts to address these challenges with improved education through working with patient support groups, annual meetings, and workshops for the duration of this project, we can raise awareness, train next-generation clinicians in addition to fostering collaboration across disciplines.

3 Epigenomics Rare Diseases Node

Lead applicant: **Professor Michiel Basson, King's College London**

Abstract: This node will coordinate research in the domain of epigenomics of rare diseases. Understanding of epigenomics of rare diseases is likely to be crucial for the translational aspects of many rare diseases, thus this node will be a critical component to the broader rare diseases landscape.

We have assembled a multi-disciplinary node team including experts in epigenomics and epigenetics, human genetics, animal models, pluripotent cellular models and neuroimaging with significant track records of studying rare epigenetic disorders. The initial team encompasses institutions across the UK and investigators at different career stages, as well as industry partners. The node will build upon >£15m existing relevant research funding and connect to several existing investments of >£100m, including from the NIHR and MRC. This node will provide epigenetic expertise for pre-clinical, translational and clinical research in rare diseases and will collaborate with other nodes to develop future projects in this domain.

We will also actively support and enhance training opportunities for postgraduate researchers and deliver networking opportunities by hosting an annual Epigenome node meeting to bring together fundamental and clinician scientists, clinicians, technical and methodological experts, and patient groups that will evolve into an international 'Epigenomics of Rare Diseases' conference.

Our initial focus will be on rare epigenetic disorders which include monogenic diseases with mutations in genes encoding direct chromatin modifiers or remodellers and multi-locus imprinting disorders (MLID). Collectively, this group of epigenetic disorders are relatively common with major unmet clinical need due to their mechanistic basis being poorly understood, and progress in their management being hampered by the lack of known biomarkers (diagnostic, prognostic and therapeutic) and therapies. Spanning diverse epigenomic disorders, our underpinning aim is to initially tackle these challenge areas by identifying convergent molecular features and mechanisms for translation into novel biomarkers and therapeutics by using complementary, integrative, novel and bold approaches in three enabling projects - (1) Multi-omics on samples derived from patients with MLID; and understanding mechanisms and discovering treatments for chromatin disorders using (2) existing mouse models; and (3) human pluripotent stem cell derived disease models.

The main expected deliverable for the node is to establish a national collaborative multi-disciplinary network for epigenomics of rare diseases that would be an international reference on research in rare epigenetic disorders for policy-leaders and decision-makers in this field. Our project-related deliverables include to test feasibility of multi-omic profiling in samples from patients with epigenetic disorders; generate preliminary multi-omic and in vivo multimodality neuroimaging data from existing mouse models of rare chromatin disorders; and to perform comparative multi-omic analyses from human pluripotent stem cell-derived models of the same rare chromatin disorders. Our expected outputs include submission of five or more collaborative grant applications by multi-disciplinary groups from the node; and to publish three or more papers.

The expected enabling impacts of these projects are (1) to perform technology evaluation and complete data integration to develop grant application for development of diagnostic and prognostic biomarkers from patient samples for wider set of rare diseases in future projects; (2) generate data to support future grant applications using mouse and cellular models to identify convergent disease mechanism for translational and pre-clinical studies and to develop appropriate platforms suitable for drug screening; (3) to generate sharable resources for researchers studying epigenetic diseases.

4 mTOR pathway diseases

Lead applicant: **Professor Joseph Bateman, King's College London**

Abstract: The domain is the mechanistic target of rapamycin (mTOR) cellular signalling pathway. The mTOR signalling pathway is a set of molecules in our cells that sense a wide range of inputs and regulate key processes, such as cell growth and metabolism. mTOR pathway hyperactivity causes 11 rare diseases affecting 10,000 patients in the UK, including the multisystem disease tuberous sclerosis complex. mTOR pathway disease patients have a range of symptoms, from benign tumours in multiple organs, to brain malformations causing epilepsy, which can start in infancy. mTOR pathway diseases are treated independently by different medical specialities and clinics, even though they share a common cause and can potentially be treated using the same drugs. The mTOR pathway diseases node will bring together clinicians, researchers, charities, industry and not-for-profit organisations to improve the diagnosis, treatment and clinical outcomes for mTOR pathway disease patients. There are major challenges in this domain including the difficulty in identifying and engaging patients; standardising genetic diagnoses, collection and description of patient data; recruiting patients for clinical trials; obtaining patient tissue to study underlying disease mechanisms. The aims of the node are to (1) improve pathways to treatment for mTOR pathway diseases; (2) understand the mechanisms underlying mTOR pathway diseases; (3) improve diagnoses of mTOR pathway diseases. We will overcome the challenges through our networking activities and research projects. We will partner with two major UK charities, the Tuberous Sclerosis Association and Epilepsy Research UK, to recruit patient representatives who will be involved at every stage of the project and sit on the steering committee. Annual symposia will be held for all stakeholders to present results within the node, facilitate networking and drive progress in the domain. The node research will result in the first UK patient registry of mTOR pathway diseases, which will engage patients and facilitate clinical trials. We will develop resources and use state-of-the art techniques to analyse cells and tissue from mTOR pathway disease patients, which will accelerate understanding of the underlying mechanisms and lead to new treatments. The node will also propose new guidance for doctors to identify, diagnose and treat mTOR pathway diseases and investigate cutting-edge new technologies for genetic diagnosis. Over five years the node will transform the mTOR pathway disease landscape in the UK.

5 MRC Rare Disease Platform Node: Rapid Rare Disease Diagnostics and Analysis with Long Read Sequencing (RADIAL)

Lead applicant: **Professor Andrew Beggs, University of Birmingham**

Abstract: Many rare diseases are passed down through families by inheriting genes from your parents. The development of "next generation sequencing" technologies (NGS) have allowed us to discover what the causes of a proportion of these diseases. This allows us to develop new treatments which can significantly improve a patients quality of life, perhaps even offering a cure. However, despite this new technology a significant proportion of these diseases do not have any identifiable genetic change passed down when analysed by NGS. A new technology called "Long Read Sequencing" (LRS) allows a much higher resolution at detecting these changes. LRS is especially good at examining the "dark matter" of the genome, the part of the genome that can't be analysed by NGS techniques, and has identified causes for several rare diseases. Our ambition is to set up a network providing access to LRS technology, run by experts in the field, to help researchers access this new technology and use it for patient benefit.

6 Changing Clinical Practice in Rare Diseases Through Innovative Trial Designs

Lead applicant: **Professor Lucinda Billingham, University of Birmingham**

Abstract: Patients with rare diseases are entitled to receive treatments which have been approved for use by regulators based on good quality clinical trial evidence. Clinical trials are challenging to undertake in rare diseases because of the limited patient population that provide participants, and alternatives to the standard approach to clinical design are required in this setting. One approach to clinical trial design is to use a method called Bayesian statistics, whose name derives from a statistician and philosopher from the 1700s called Thomas Bayes. He devised a theorem on which Bayesian statistics is based and there is now widespread use of such techniques. This approach has been promoted for use in trials of rare diseases because it allows more flexibility for decision-making than the more rigid hypothesis testing that is more traditionally used. Bayesian methods allow cumulative learning in trials such that the results from each patient gathered over time contribute to the increasing knowledge of the experimental intervention under investigation and can minimise the total number of patients needed. Another advantage of Bayesian methods is that it allows any prior information to be incorporated into the analysis and thereby potentially reduce the total number of patients required in the trial itself.

The CAPTIVATE node aims to develop innovative clinical trial designs that enable the efficient evaluation of treatments for rare diseases with limited numbers of participants such that the design and data are acceptable for licensing by regulators; the 'fit-for-filing' paradigm. Such trials could be generating sufficient evidence to either license new interventions or license existing interventions for new indications. Bayesian approaches and adaptive trial designs will underpin the methodology required to achieve the objectives of the CAPTIVATE node.

The traditional approach of running multiple sequential phases of clinical trials is not feasible in rare diseases, particularly in those that are ultra-rare, so part of this vision is to develop trial designs that form a single study (a 'one-stop-shop') that encompasses all phases of clinical trials. The node will have a particular focus on paediatric trials in which efficient trials with limited participants are essential to ensure that beneficial treatments for children are discovered and licensed in minimal time.

The project will explore how best to develop and incorporate prior distributions such that the trial results would be acceptable by clinical communities, patients and regulators. In the paediatric setting, there is often relevant data from adult clinical trials that could be incorporated as priors but there is limited practical implementation of such an approach and further investigation is required. Licensing treatments generally requires data from randomised controlled trials but incorporating a concurrent randomised control arm may not be the best use of the limited number of patients available so we will explore how historical control data may be generated to be acceptable to regulators.

The CAPTIVATE node will bring together the UK's leading trial methodologists with clinical researchers experienced in rare diseases, industry partners, regulators and patient representatives to develop and discuss trial designs that could deliver the level of evidence required for licensing in this setting. This network of experts will develop innovative designs and guidelines that could enhance the approach to clinical trials for rare diseases and thereby improve the healthcare of these patients in the future.

7 Eye Cancer tissue and imaging Artificial Intelligence Database and bioresource (Eye-CAN-AID)

Lead applicant: **Professor Sarah Coupland, University of Liverpool**

Abstract: Importance. Eye cancers can affect many parts of the eye. They are rare, with ~900 new cases every year in the UK. The death rate from eye cancer can be as high as 50%, or as low as 4%, but all eye cancers can potentially cause blindness, visual impairment and or facial disfigurement. These negatively affect quality of life for the patients and their families. We urgently require improved treatments, and also better ways to detect eye cancers, enabling earlier treatment.

Background. Biobanks store biological samples, such as blood, tissue left over from surgery, or medical images, with the permission of donors. The information in biobanks enables researchers to develop new ways to detect, diagnose and treat disease. For rare diseases, it is essential that the biobank is UK-wide to collect enough samples to take advantage of analysis technologies that could yield important new insights. For eye cancer, the closest thing to such a biobank is the 15-year-old Liverpool Ocular Oncology Biobank. This focuses on one type of eye cancer, in patients treated in the 'catchment area' of the Liverpool Ocular Oncology Centre; the western third of England. Other UK biobanks focus on common cancers and life-threatening diseases. Collection of samples and research in rare eye tumours is disjointed creating a missed opportunity for advancing research in these diseases.

Our vision. We aim to link the UK specialist NHS eye cancer centres, promoting best practice in biosample and medical image collection and data sharing in five rare eye cancer types, which affect adults and children, for use in future research. We will strengthen links between centres to develop a national bioresource and database (Eye-CAN-AID), to catalyse research in these rare tumours, and improve patient care.

Our approach. We will build on existing collaborations with partner NHS Trusts in the UK to deliver a step change, expanding from 'NHS service provision' only to create a true national eye cancer research community with close incorporation of patient advocates. We will use the 'know-how' and framework of the Liverpool Ocular Oncology Biobank, and of national image collaboratives and Biobanks, to build on existing infrastructure and establish best practice for sharing data, while developing ethical frameworks and maintaining public trust. Eye-CAN-AID will collect high-quality clinical samples, images and data from patient donors with their permission, for use in research. The platform will ensure security and patient confidentiality, and will follow procedures that meet national and international standards, ensuring that the samples and data can be used for high quality research. The resource will support new research using artificial intelligence to analyse images for early signs of eye cancer. It will also enable research to develop tumour 'organoids' - research models, which can be grown in the laboratory overcoming the limitations of the rarity of clinical samples. These organoids could then be used by others in drug discovery research and testing.

Working with others. We will foster a patient-oriented research community to encourage patient, clinician and scientist participation in Eye-CAN-AID and ensure that our resources answer the questions that are important to patients. Our patient voices will include those from existing national organisations involved in eye cancer patient care and support.

Impact. Eye-CAN-AID will offer reliable, and long-term storage of clinical images, cancer samples and linked data from five types of rare eye cancer. These resources will be connected with a network of contributors and researchers to enable research and discovery. This will empower much needed research in

-Understanding the genetic causes of all eye cancers

-Developing new biological 'markers' to predict which treatments will be effective

-Using artificial intelligence to detect early signs of cancer in eye images

-Personalising treatment

14-12-2022

8 Lipidomics and metabolomics for rare disease diagnosis

Lead applicant: **Professor William Griffiths, Swansea University**

Abstract: Mass spectrometry (MS) offers high specificity of metabolite identification and quantification and is routinely used for newborn screening to monitor six inherited metabolic disorders. Recent advances in MS based metabolomics and lipidomics allow the quantitative profiling a large number of metabolites in a given sample. It is a powerful tool to facilitate rare disease diagnosis in combination with genomics and other biochemical assays. This application will bring expertise from the UK lipidomic/metabolomic community into the domain of rare disease diagnosis. It will translate the latest knowledge and methods from research settings to the clinical laboratory. Each of the aims detailed below will be delivered by the close collaboration of academic experts with clinical scientists, geneticists, clinicians, patients, carers and rare disease charities.

Our specific objectives are to:

*Set-up a UK node for the metabolomic and lipidomic study of rare diseases leading to faster and more secure diagnosis and monitoring.

*Generate a publicly available metabolite database specific for rare diseases.

*Compile a mass spectrometry spectral library for rare diseases.

*Publish guidelines for the reporting of lipidomic/metabolomic data for the diagnosis of rare diseases.

*Establish a best practise model for specialised clinical laboratories to provide a metabolomics service for the diagnosis and monitoring of rare metabolic disorders so there is a planned service and not a random approach.

Our research challenges are to (i) translate and improve screening assays for rare lipid and metabolic disorders from research tools used in academia into robust and cost-effective clinical tests, and (ii) to prove that utilisation of a lipidomic/metabolomic approach can lead to improved diagnosis for patients.

Ultimately our studies will lead to an improved understanding of the application of lipidomics/metabolomics and its utility to a group of patients who are suspected to suffer from a rare disease but have not yet received a diagnosis. This is important going forward so that there is a planned diagnostic service for such patients and not a random approach.

The node will be open to new members who bring in different omic expertise including bioinformaticians and economists, also to clinical centres with the challenge of diagnosing patients with rare metabolic disorders.

9 Towards Precision Medicine for Rare Disorders causing Immunodeficiency, Autoimmunity or Autoinflammation (RADIAN)

Lead applicant: **Professor Sophie Hambleton, Newcastle University**

Abstract: We propose to establish a node focused on RAre Disorders causing Immunodeficiency, Autoimmunity or autoinflammatioN (RADIAN). This is a large group of conditions, some genetic in origin, in which a faulty immune system leads to problems with infection, inflammation and/or resulting tissue damage. Often these are very debilitating, severe and life-limiting conditions that are difficult to treat.

Over the past few years, a lot of effort and resource has gone into molecular diagnosis in patients with RADIAN but that is just part of the story. Only a minority of patients have an identifiable genetic condition, and too often such a diagnosis fails to translate to better therapy. We know there is lots of overlap in symptoms, disease mechanisms and treatments among patients with different disorders, including those with and without genetic causes. On the other hand, the same disorder can reveal itself with different problems to different clinical specialties.

Our plan is to work together across disciplines to drive "precision medicine" for these diseases, targeted to underlying causes. First and foremost, we will connect patient groups and diverse clinical teams with basic scientists and analysts. This collaborative approach will enable us to make the best use of existing knowledge and resources, including data already held about the same patients in different research projects. With help from the James Lind Alliance, we will develop shared research priorities and endeavour to underpin them by fulfilling the following unmet needs:

1. Join-up between separate research projects involving the same patient group We will build on prior research projects and registries, each of which has generated separate datasets. We propose to work with patient organisations and informatics experts to establish a secure, enduring and ethically acceptable data integration framework, bringing these resources into alignment. We will partner with HDR UK and the National Congenital Anomalies and Rare Disease Registration Service to help us develop and maintain this important registry. We will work with others across the RDRP who will likely be attempting the same in other rare diseases.

2. Enhanced capacity for functional testing to inform diagnosis and treatment For rational treatment choices, we need to group patients who are similar. At present this is done largely on the grounds of genetic diagnosis or symptoms. To refine this classification and predict response to treatment, we will develop new tests to tease out how well immune cells function in the test tube. The same tests could help confirm the significance of genetic changes in individual patients (potentially clinching diagnosis), or even the effectiveness of targeted therapies. The latter might include new drugs or established ones that could be put to use in RADIAN patients.

3. Readiness for clinical trials In rare diseases, it is usually impossible to carry out randomized trials comparing treatment against placebo in a large number of patients. However, there are other approaches towards gathering good quality evidence of a treatment's effectiveness. For example, we might group together patients with similar patterns of immune cell (dys)function, measuring the impact of a given therapy or series of treatments in systematic way. We will make a start by developing the right measures, learning how best to group patients together and working with clinical trials experts across the RDRP to prepare for future clinical trials.

By providing a landscape view across the UK RADIAN cohort, we will empower: (1) better genomic interpretation and disease gene discovery in monogenic cases, (2) better stratification of disease and treatment response, resulting in (3) new opportunities for therapeutic intervention. At the same time we will educate and inspire the next generation of clinicians and researchers to carry forward these goals in partnership with patients and industry.

10 A rare disease platform for immune haematology and haemolytic red cell disorders

Lead applicant: **Dr Quentin Hill, Leeds Teaching Hospitals NHS Trust**

Abstract: The rare disease platform for immune haematology and haemolytic red cell disorders aims to better describe, diagnose and manage a group of more than 17 rare acquired and inherited disorders of red cells and platelets. These conditions include the acquired bleeding disorder immune thrombocytopenia (ITP) as well as autoimmune haemolytic anaemia (AIHA), an acquired immune red cell disorder that causes anaemia. Hereditary haemolytic anaemias (HHAs) arise from abnormalities in the red cell membrane, or the enzymes or haemoglobin inside red cells.

Although there are many ITP treatments, there is little data comparing these, and we will analyse real world evidence from over 5000 patients in the existing adult UK ITP registry to compare treatment responses and seek to identify patient sub-groups, some frail, who may benefit more or less from specific, often costly treatments. We will work with NHS Digital to extract and analyse national data on all these disorders to understand disease burden, identify future research questions and explore co-ordination with our registries to maximise their efficiency. Learning from COVID studies, we will design an adaptive trial that can flexibly compare multiple drugs across several conditions (ITP/AIHA) in preparation for future funding applications.

Steroids are used up front and frequently at relapse in ITP and AIHA, but patients dislike steroids more than alternatives and doctors often underestimate side-effects. We will seek an accurate laboratory predictor of steroid response so that patients unlikely to respond can try alternatives. The test may also predict steroid response in other rare diseases. We will also explore an accurate diagnostic test for ITP as there is currently none and some non-responding patients are later found to have a different cause for low platelets. In addition, we will introduce genetic testing to ITP/AIHA patients to increase diagnostic accuracy, as well as to better understand the causes these disorders. We will set up regional clinical meetings to discuss patient care and who is suitable for genetic testing. If genetic tests are useful, they will be introduced into routine NHS care and the meetings will continue after this study finishes, giving access to best care to patients living farther away from academic hospitals.

Finally, we will establish a registry for children and adults with AIHA and HHAs. There is no clinical network or patient support groups for these conditions and less is known about their disease burden, treatment and outcomes. We will apply experience gained in ITP care to the registry, and we know from previous work that patients with these disorders consider a registry a care priority, and that clinicians want to support registry enrolment. Understanding the impact of treatment on quality of life (QoL) is another patient priority and we will ask participants to complete QoL questionnaires during visits. Similar to the ITP registry, we will look for sub-groups of patients who may benefit more or less from certain treatments, and data we collect may be helpful for the approval of new drugs for NHS use, since patient numbers in trials for rare conditions are often low. We will also explore the benefits and burdens of blood transfusion to guide our routine and emergency practice. It is hoped that through patient representation and supporting clinical sites, new networks will develop, and we will seek commercial and non-commercial funding to extend the registry.

We believe that these projects, undertaken together, will complement each other, with experience from a more established rare disease network (ITP) supporting development of less established conditions (AIHA/HHAs). By developing registries and clinical networks to support vital laboratory studies, alongside an adaptive trial design, our goal is for patients to receiving the correct diagnosis, followed by the best treatment, tailored to their specific circumstance

11 MRC Neurogenetics Node: A network to identify, define and investigate rare undiagnosed neurological disorders

Lead applicant: **Professor Henry Houlden, University College London**

Abstract: Over half of known inherited disorders impact on the nervous system and one in six of the population will suffer from a neurological condition. The Genomics England (GEL) 100,000 Genomes Project (100K) was a step-change success, in identifying patient groups and genetically defining rare diseases. Neurology was the most successful, recruiting over 24% of all rare disease participants. The average rare disease diagnostic rate was 25% in the 100K, but this still leaves 75% of probands without a diagnosis: leading to inadequate patient management and no chance of entering a genetic defect-based treatment trial.

This relatively low diagnostic rate can be extrapolated to ongoing rare disease diagnostic sequencing and therefore improvements are paramount. Deficiencies in the 100K include lack of UK wide co-ordination and phenotyping of undiagnosed disease subgroups, as well as the integration of existing sequencing methods with new long-read sequencing in negative cases.

Therefore, our goal is to develop a new, highly coordinated MRC Neurogenetics Node, to identify, collate, phenotype and take additional biosamples on rare, likely-genetic undiagnosed neurological disorders. We will build a UK wide clinical team to work with genome associates and the Node coordinator. We benefit from widespread connectivity to existing academic centres, grant funding, patient societies and established infrastructure to facilitate networking and coordination activities. Families will be databased and clinically separated into neurological disease cohorts. Previous DNA sequencing data will be reassessed, variants of unknown significance (VUSs) affirmed or rejected, and in collaboration with Genomics England integrate genome with transcriptome (expressed regions) and long-read sequencing, employing the most advanced diagnostic techniques.

Main objectives divided as three overlapping projects.

Project 1: The Neurogenetics Network for recruitment, early diagnosis and identification of rare disease subgroups. Neurogenetic clinicians, with have support from genome associates to recruit, phenotype, REDCap database and collect additional biosamples. The clinical phenotypes of undiagnosed rare neurological disease subgroups will be important for stratification, as well as produce subgroups for clinical interrogation. Deliverable examples include rare disease extended phenotypes, screening and treatment response.

Project 2: Bioinformatically interrogate undiagnosed rare neurology patient genomes, a limitation of the 100K and subsequent exome and genome sequencing is that families are not re-investigated bioinformatically, but with the increase in family members and clinical details from the network, will likely increase diagnostic yield, confirm or reject VUSs and the network will collect further biosamples from family members for segregation and transcriptome sequencing to increase the percentage of diagnosed patients.

Project 3: Integration of long-read sequencing. Many undiagnosed, short-read genome sequencing negative cases are caused by previously missed, expansions or rearrangements, particularly common in neurological disorders. In the most promising families identified in the Neurogenetics Node, we will work with Genomics England (collaborators) to integrate short-read genome and transcriptome sequencing, initially targeted, and later whole genome long-read PacBio or Nanopore sequencing. Initial deliverables will include long-read analysis of the newly identified expansions and later the use of whole genome long-read sequencing to identify previously camouflaged genetic causes such as novel repeat expansions and rearrangements.

Our project challenges could not have been met in the past as we lacked an undiagnosed rare neurological disease network to deliver family collection and phenotyping. Combined with the integration of transcriptome and long-read sequencing we are confident we will genetically define many unresolved families.

14-12-2022

12 A North East and Yorkshire node for rare recessive conditions: consolidating public partnerships, diagnostics & research in genomic science

Lead applicant: **Professor Colin Johnson, University of Leeds**

Abstract: In response to the recent establishment of the NHS Genomic Medicine Service and the commitments of the Rare Diseases Action Plan (2022), we propose a platform node within the Rare Disease Research Platform that focuses on improving the clinical utility and potential translation of genomics in the clinical area of rare recessive conditions. Whole genome sequencing (WGS) remains an immensely valuable clinical and scientific resource with huge potential benefits for patient groups, resulting from improved molecular diagnoses and opportunities for personalized medicine. However, these benefits are yet to be fully realized because, for example, the current tiering software tools/filtering for recessive variants provided by Genomics England (GeL) are likely to miss clinically significant changes. In addition, the current timescales for NHS reporting of WGS can lead to some with treatable genetic disorders suffering from delayed diagnosis and access to therapy or targeted clinical management. Current NHS rapid testing pathways are strict in their eligibility criteria so that only those children acutely unwell (for example, in the neonatal intensive care or paediatric high dependency units), or families where there is an active pregnancy, can be considered. This leaves a dilemma for clinicians in prioritising standard or semi-urgent testing for those not falling into those groupings (e.g. children with progressively worsening seizures whose treatment options can be influenced by genotype). In the North East and Yorkshire, we need to address pressing and important clinical needs for our local patients and families in improving the diagnosis, management, treatment and understanding of rare recessive conditions in the post-genomic era, as well as improving equity of access to genomic services. Our platform node will address these challenges by creating new opportunities for consolidating and enhancing our existing strengths in communication through multi-disciplinary teams (MDTs), research & training activities between fundamental researchers and clinicians, and development of innovative diagnostic methodologies using genome sequencing and disease modelling. Our node team has a long-established record of engaging with under-served communities and, as a priority for all activities of our node, we will work together with local communities to explore the best ways in which we can address their specific needs around communication and understanding of genetic diseases. We will ensure that patient & public involvement and engagement is meaningful and actionable, in order to achieve the overall aim of the node to enhance links between NHS Genomic Testing Delivery and academia. We envisage that our node will leverage improved diagnostics through research expertise and collaboration to deliver the best genomic medicine across the UK, in direct conjunction with the NHS clinical services and, in particular, through long established links with the three clinical genetics teams in the region. We will develop the node into a national MDT/referral centre for rare recessive conditions supported within the Rare Disease Research Platform. In the longer term, our activities will support the "genomic transformation" of the NHS into the world-leading healthcare system that integrates cutting-edge genomic technologies to predict and diagnose inherited rare recessive conditions, and to personalise treatments and interventions. More generally, we envisage that our node will enable under-served patient groups to better access the full benefits of research studies in the post-genomic era.

13 Rare cystic lung disease mechanism and phenotyping node

Lead applicant: **Professor Simon Johnson, University of Nottingham**

Abstract: Rare cystic lung diseases are a group of conditions which cause progressive lung damage resulting in breathlessness, lung collapse and in some cases death due to respiratory insufficiency. Rare cystic lung diseases include four better described diseases, lymphangioleiomyomatosis (LAM), Birt Hogg Dubé disease (BHD), pulmonary Langerhans Cell Histiocytosis (PLCH), lymphocytic interstitial pneumonitis (LIP) and a larger number of less well recognised and poorly understood conditions. Most of these diseases also cause problems outside the lungs including tumours which lead to high health burdens for patients. Like many people with rare diseases, these patients experience long delays to get the correct diagnosis, feelings of isolation that comes with a rare diagnosis and often find it difficult to access specialised care. The proposed Rare Cystic Lung Disease Mechanism and Phenotyping Node will link expert health centres, laboratory and data scientists, health technology companies and patient organisations to facilitate rare disease research by improving diagnostic methods and developing personalised care predictions and therapies for RCLDs whilst contributing methods which can be used to advance research and care in many rare diseases. We will do this by linking detailed patient characteristics (phenotyping) with blood, genetic and tissue samples which are linked to continually updated patient outcome data, including measurements and symptoms recorded remotely by the patient at home. By collaborating across rare disease centres, other respiratory services and lung transplant units we will maximise patient recruitment and rare tissue sample collection allowing the creation of the most detailed national research database and resource for cystic lung diseases. By incorporating laboratory scientists, the node will develop new laboratory methods to model and study how the lungs are damaged in rare lung diseases using stem cells and rare disease tissue which can be used to identify drug treatments. By applying artificial intelligence analysis to patient, blood, genetic and other data obtained through the node, we will identify groups of characteristics associated with particular diseases and disease outcomes to improve the diagnostic process and develop tests predictive of outcome with which to improve patient management and personalise treatment decisions. In collaboration with patientMpower, a digital health technology company, we will use home monitoring of lung function, oxygen saturation activity and symptoms to open rare disease research and care to patients in difficult to reach communities and those unable to travel to a centre allowing doctors to detect changes in clinical state sooner and more easily than in the standard care model. Using existing NHS rare disease and X-ray data we will develop methods to identify patients with rare cystic lung diseases who have not yet been diagnosed and understand their care patterns to improve rare disease services. Additional activities of RCLD node clinicians, will be to develop clinical guidelines for the workup and diagnosis of RCLD and develop a rare lung disease training program for respiratory clinicians. Working with patient organisations, specialist societies and commissioning groups we will embed these improved pathways into clinical care to sustainably grow rare disease research which delivers patient, economic and societal benefits.

14 DAIRD: standardising Data and embedding Artificial Intelligence for Rare Diseases

Lead applicant: **Professor Amy-Jayne McKnight, Queen's University of Belfast**

Abstract: DAIRD is a UK-wide partnership that will unlock the power within health and social care data to facilitate evidence-based healthcare, advance understanding of rare diseases (RDs), and improve care for patients and their caregivers.

RDs are a major public health issue with ~450 million people affected globally. There are almost as many people living with RDs as there are with diabetes, yet RDs receive much less support. Many RDs are chronic, complex and associated with physical, intellectual, and/or neurological disabilities. Many people living with RDs lack peer and community support. ~70% of RDs affect children; >60% of children who die under the age of 15 years have a RD. Compelled by necessity, the RD community are often pioneers developing creative and innovative health and social care transformations that benefit the wider populace. DAIRD is a crucial node within the UK RD platform, helping address global RD challenges and strategically targeting local priorities.

Approximately 4 million UK citizens are living with RDs and significant unmet health and social care needs. On average, RD patients in the UK experience 3 misdiagnoses, visit 7 different doctors, wait >4 years before receiving a diagnosis and attend multiple medical specialities, with many never obtaining a name for their condition. NHS costs for patients with undiagnosed RDs was >£3.4 billion in the 10 years prior to diagnosis. Without a diagnosis people struggle to obtain the right treatment, understand how their condition will develop, connect with relevant support, and the NHS cannot adequately plan services. We do not know the number of people diagnosed with individual RDs across the UK; many RD diagnoses are effectively invisible to our health and social care systems.

Artificial intelligence offers significant potential to enable a more personalised model-of-care based on each individual's characteristics and predictions of their health trajectory. It may inform clinical decisions about necessary tests, diagnosis, clinical visits, condition flares, and treatment regimens, improving safety and empowering patients to make better informed decisions about their healthcare, improving patient outcomes, and reducing the burden of living with a RD. We will work with stakeholders including patients and patient groups, the general public, RD implementation groups across the UK to ensure data is used transparently and responsibly within legislative guidelines for each country. DAIRD will:

1) Establish UK-wide RD registry infrastructure to make high-quality data more accessible and accelerate RD research.

2) Connect data silos for RD, minimising technical barriers to finding and accessing RD data. We will use intelligent data-driven tools to manage complex real-time data and develop informed solutions that save lives. We will look in medical records to identify 'invisible' people with exemplar RDs; we can potentially make a diagnosis many years earlier which avoids unnecessary referrals, clinic visits, and a long costly diagnostic odyssey for patients and healthcare providers. DAIRD will help identify prospective participants for research project based on explicit phenotypic or genetic characteristics. Minimising manual data collection and analysis enables NHS staff to focus more on direct patient interactions.

3) Host a knowledge exchange portal and establish a virtual community of practice to optimise knowledge, skills, and the implementation of evidence-based practice.

4) Empower clinicians to identify which patients would benefit from genetic testing, to choose the right genetic test, understand results, and seek more expert advice. Analysing more laboratory-based results such as genetic, biochemistry and imaging data together with doctor's notes (known as 'multiomics') will speed the path to diagnosis, improve understanding of individual RDs, and suggest new therapeutic targets.

15 Ethical Legal and Social Issues (ELSI) in Rare Conditions Research and Clinical Practice

Lead applicant: **Professor Ramona Moldovan, Manchester University NHS Fdn Trust**

Abstract: Genomic technologies hold great promise to bring benefits for individuals and families living with rare conditions (RC) in terms of diagnosis and treatment. However, the Ethical Legal and Social Implications (ELSI) of genomics have received less academic, public and professional attention. Building upon existing multi-disciplinary clinical, scientific, bioethical and methodological expertise we aim to focus on and promote progress in areas of long-standing concern, such as consent to testing or participating in clinical trials, living with undiagnosed RC, identifying barriers to mainstreaming genomic testing, the psychosocial impact of RC, the design of clinical trials for treatments of RC.

16 Early assessment, diagnosis and treatment of Parkinson's Plus Related Syndromes (ExPRESS)

Lead applicant: **Professor Huw Morris, University College London**

Abstract: Progressive supranuclear palsy (PSP), Multiple System Atrophy (MSA) and Corticobasal syndrome (CBS) are rare, but devastating disorders of high clinical need and poor outcomes. The last decade has seen rapid progress and recognition that PPS are not only tractable disorders in their own right, but also provide ideal demonstrator conditions in which to test therapeutic strategies of potential wide impact to dementia and movement disorders. Here we plan to leverage scientific and organisational opportunities in the UK, to transform diagnosis, prevention and treatment for PPS. We will do so in partnership with NHS and charity services supporting families affected by PPS including the Progressive Supranuclear Palsy Association (PSPA) and Multiple System Atrophy Trust (MSAT) and by engaging the national research platforms for discovery science and translation, including the Dementia Research Institute (DRI), Dementia Platform UK (DPUK), and National Institute for Health Research - CLinical Research Network and Biomedical Research Centres (NIHR - CRN/BRC). In addition a number of drug companies have indicated that the would like to collaborate in this initiative.

A major challenge for PPS research progress has been to build the infrastructure required to enable national network activities and nationally-representative patient recruitment. UK charities helped to establish a skeleton network of UK sites (the PSPA and MSAT funded PROSPECT-M study) which has been successful in proof-of-concept for recruitment and coordination across specialist clinics. There is significant interest from both pharmaceutical industry and university researchers in developing new trials of disease modifying therapies. This calls for new diagnostic markers (for example specialist blood tests, spinal fluid tests, and pathology-specific brain scans).

To maximise the impact of forthcoming trials, we need to meet the challenge of recruiting patients with early stage diseases, improving diagnostic and prognostic accuracy and developing new trajectory models for individualised approaches.

Within our proposed ExPRESS (Early assessment, diagnosis and treatment of Parkinson's Plus Related Syndromes) study we will link together clinicians and therapists who see patients with early stage disease and establish collaborative links with disease charities (PSP Association, MSA Trust). We will link together with professional bodies (Association of British Neurologists Movement Disorders Group, British Geriatric Society Movement Disorders Group), industrial partners and linked UK scientific research consortia such as the UK Dementia Research Institute (DRI), Dementia Platform UK (DPUK), UK Brain Bank Network (BBN) and Health Data Research UK (HDRUK) to maximise the scientific potential of the UK's activity in this area and to improve the potential to develop new treatments.

17 Enhanced Variant Classification Rare Disease Node

Lead applicant: **Professor Andrew Mumford, University of Bristol**

Abstract: The NHS has revolutionised genetic diagnosis of patients with inherited rare diseases (RD) by establishing a network of Genomic Laboratory Hubs (GLHs) that use state-of-the-art technologies to detect changes in the sequence of DNA from patients called variants. Although most RD are caused by just one or two variants, patient DNA samples always contain multiple variants, the majority of which are incidental discoveries with no health implications. As part of each genetic test that is performed, GLH scientists must distinguish carefully which variants are the cause of RD and which are incidental discoveries. This process of variant classification is time consuming and is frequently inconclusive meaning that potentially helpful genetic test results cannot be returned to patients.

We have assembled an Enhanced Variant Classification (EVC) node that brings together computation experts, clinical scientists and researchers in genomics and healthcare science to relieve the classification bottleneck in genetic testing. The team will address this challenge by developing a suite of new computational tools based on a proven method called FATHMM that uses machine-learning to predict whether variants observed in patients are harmful or not. We already know that FATHMM is effective in the complex field of genetic diagnosis in cancer and for some RD applications. The EVC node will extend this significantly by developing and testing a new generation of FATHMM methods for a much wider range of variants that are common in RD patients. The main aim of the EVC node is to develop powerful variant classification tools that when used alongside current techniques, will increase the number of RD genetic test requests in which a confident finding can be returned to healthcare professionals and patients.

There will be three interrelated research projects. First, a suite of prototype FATHMM methods will be developed that target different kinds of variant that are currently difficult or impossible to classify with current methods. These methods will then be tested using variants identified by the GLHs from patients with a cross section of different RD. The results obtained using the new FATHMM methods will be compared to results of detailed evaluation of the variants using national genetic databases such as the NIHR RD BioResource, National Genomic Research Library and UK BioBank and experimental results from a network of research laboratories. This research information will be used to adapt the new FATHMM methods to progressively improve performance. In the third research project, we will compare how well the fully optimised FATHMM methods improve genetic testing in the GLHs when included alongside current techniques. This project will focus on the end-to-end process of genetic testing, the cost effectiveness of testing and the perceptions of patients and healthcare professional. We expect this research to transform variant classification and thereby to improve patient care by increasing the performance genetic testing for RD patients in the NHS and elsewhere.

The EVC node will be supported by a network of organisations and expert advisors to help ensure that the research aligns with the needs of the NHS GLH diagnostic service and can be used to improve the service going forwards. The EVC node will work closely with other nodes in the national RD platform, particularly those looking at other ways of improving diagnostic tests and evaluating impact on wider NHS services. The experimental investigation of whether new variants cause or do not cause different RD will also provide important new information about the relationship between gene sequence changes and different RD and about underlying RD mechanisms.

18 National Adeno-associated virus (AAV) Gene Therapy Node for Rare diseases (NAN4RD)

Lead applicant: **Professor Amit Nathwani, University College London**

Abstract: Gene therapy is an exciting new treatment that offers the potential to cure or provide long-term benefits for rare inherited conditions. In many rare disorders, individuals inherit a problem in a gene which stops it from working. Gene therapy works by delivering a normal copy of the disease-causing gene to recover the function of critical proteins. This treatment is given as an injection in the hospital and is a "one and done" treatment. Gene therapy is based on a harmless natural virus called adeno-associated virus, or AAV. A manmade version of AAV has been carefully engineered to make it into a vehicle able to carry new genetic treatments. These AAV vehicles, can be used to deliver a normal copy of this gene into specific cells in the body. Gene therapy has gone through extensive and rigorous testing over the last twenty years. After successful clinical trials, gene therapy has been given the green light for use in three different conditions in Europe. These include rare disorders affecting the nerves, blood or eyes. One of the first of these was made available on the NHS last year for treatment of young children with Spinal Muscular Atrophy, a serious and progressive disorder affecting the nerve and muscles. Other conditions where gene therapy has been approved, are in the severe bleeding disorder, haemophilia and in the sight disorders, Leber congenital amaurosis. This is only the start, and we expect many more rare conditions will be treatable with gene therapy by 2025.

Gene therapy is a very different form of treatment compared to conventional therapies and to allow safe and fair access to gene therapy for the rare disease community we need to make changes to how our current healthcare systems work across the UK. We are setting up a team of experts in gene therapy and different areas of medicine as well as patients and representatives from the rare disease community to share their experience. This means we develop an efficient process for accessing gene therapy and continue to provide state-of-the-art care after gene therapy, allowing us to closely monitor the impact of this treatment. This will help individuals considering gene therapy receive the support they need through the entire treatment process and follow up. Our long-term goal is to develop a new system to co-ordinate care between specialist regional "hubs" and local "spoke" centres, to allow more convenient follow up.

Although we have a great deal of information about gene therapy from the trials, we still need to understand more on how these treatments will work in routine care. By studying gene therapy in different rare disorders, we will be able to develop new tests to help monitor treatment and identify problems early. A central part of the project is to set up a secure national library of samples and data from individuals treated with gene therapy. This will allow us to rapidly respond to these future unknowns and support research to improve treatments. A big unknown for gene therapy is what to expect in the long-term. We know that this treatment can work for at least decade, from one of the first gene therapy studies carried out by our team. We do not know though if gene therapy can last for a lifetime, or if there are differences between different gene therapies. In our study after more than ten years, we have not seen any major problems, but more we need more information on if problems occur rarely, and if so why. With cutting edge techniques that we are setting up we will gain detailed information on how gene therapy works long-term. This will allow us to guide how we should follow up individuals treated with gene therapy. Finally, this type of gene therapy will be the first of many types of more complex treatments that will be available in the next few years. By putting together teams such as this network, we think this this will provide a way to allow us to provide world-leading care for individuals with rare disorders in the UK.

19 Rare early onset lower urinary tract disorders

Lead applicant: **Professor William Newman, The University of Manchester**

Abstract:

The problem.

Many children in the UK suffer with significant bladder problems that result in bed-wetting, incontinence, urine infections and even severe kidney damage. In fact, rare bladder conditions are the commonest cause of kidney failure in children who can only be kept alive by dialysis and transplantation. Up to one in three children with severe bladder emptying problems also have constipation. Bowel and bladder problems have more impact than almost any other medical condition on children's self-esteem, education and social relationships.

Our approach to the problem.

Genes are the inherited instructions in our cells providing the information for how our bodies develop. We know that many genes are important in how the bladder and ureters (tubes connected to the kidneys) develop and work. We have discovered changes in a number of these genes in children with severe bladder problems. However, we have collected samples and clinical information from many children where we still do not have a genetic answer. This represents a significant unmet need. Through this rare disease node we will create a network of clinicians and researchers across the UK to collect samples and information from children affected by these conditions. We will work as a collaborative team to address these challenging problems and train and support the next generation of researchers and clinicians to care for affected families.

We propose three answers: 1. to use a new type of genetic analysis called 'whole genome sequencing', where we can study all of the genetic material in a cell, to find the causes of severe inherited bladder problems; 2. to look at how genes are switched on and off in the bladder and ureters in children from samples taken at surgery and compare these patterns to healthy children. This will give us an insight into how the organs develop and how and why this may go wrong; and 3. we will look at new exciting ways to deliver genes to the body so that they may correct these conditions using an approach called gene therapy.

Finding the responsible genes will allow us to: 1. give families the reason for their children's problems; 2. do simple genetic tests on other family members to see if they may require check-ups to detect and prevent the progression to severe bladder and kidney disease; and 3. start to understand the reasons that children are affected by these problems which will help to develop novel treatments. Furthermore, understanding rare inherited types of bladder problems can provide reasons as to why children have more common problems like bed-wetting and urine infections, which affect nearly one million UK children.

We will organise meetings with affected families to discuss our work and seek input to guide the way that we approach these studies and share information about them through charities like ERIC, the Children's Bowel and Bladder Charity. The 2018 NHS England guidance on Excellence in Continence Care highlights the inequalities and need for improvements in clinical care for individuals with urinary and bowel incontinence.

Because severe inherited bladder disorders can affect multiple family members their impact is greater. As most are inherited in an 'autosomal recessive' pattern (a genetic change inherited from each unaffected parent), these conditions are more common in communities where marriage within families occurs. In the UK there is a significant burden in families of Pakistani origin. In the Health Profile for England Report 2017, there was a threefold increased infant mortality in British Pakistanis and other measures of poorer health in this community. Therefore, supporting research in these disorders will have a major health benefit in a disadvantaged community.

20 Advanced Translational Technologies for rare Epilepsies and Neurodevelopmental Disorders

Lead applicant: **Dr Peter Oliver, MRC Harwell**

Abstract: Many diseases begin in childhood and consequently have a profound effect on patients and their families' lives. Some of these occur only once in a few thousand people; yet, although they are rare individually, there are many hundreds of rare diseases that can be passed-on through a family line. Of these genetic paediatric disorders, the majority are characterised by serious neurological symptoms such as epilepsy and developmental delay. Thanks to access to DNA sequencing, clinicians can often identify the likely genetic cause of these conditions; however, that does not always help in providing a curative treatment and there is still so much to learn about the function of genes in the nervous system.

There is now some hope in the rare genetic disease field for treatments that are targeted specifically to an individual or a small group of patients with a shared genetic cause. New technologies utilise short DNA fragments to control or even repair how a defective gene functions and these can be delivered to a patient in a similar way to a conventional drug. These nucleic acid therapeutics (NATs) are still in early development, but one valuable way to test their potential effectiveness is to take skin cells from a patient to make brain cells in a dish. These cell lines can then be manipulated to model many fundamental aspects of a human brain - with different cell types growing and connecting together in three-dimensions - as a platform to measure complex cell functions that relate directly to symptoms. The challenge is to increase the efficiency and effectiveness of this pipeline - from patient identification to a proven therapeutic strategy.

The overall aim of this proposal is to address this important challenge in rare childhood neurological disease, by bringing together a leading group of UK experts across neuroscience. We include clinical geneticists that identify new causes of paediatric disease, neuroscientists that study complex neuronal cell functionality in human cell-derived models, and team that create state-of-the-art NAT technologies. The proposal is split over three focussed projects, each over two years. First, we will establish better-standardised brain cell modelling methods by improving ways to quantify cell function - such as structure and electrical activity - that are relevant specifically to neurological symptoms such as epilepsy. Next, we will use this platform to test selected NATs in cells derived from patients and determine whether the defective cellular features detected can be reversed. Thirdly, data scientists will integrate the findings across all the projects to help us to further improve future therapeutics and better predict their effectiveness. We aim to discover at least two new therapeutic strategies for rare paediatric disease during the project.

A further essential feature of the proposal is engagement with families and the wider community to raise awareness of rare disease in the general population. This is important, not only to find those that would benefit from shared support networks, but also to educate how treatment options might be changing in the future and how families can play an important part. We will link-up with disease-associated charities, such as Epilepsy Research UK, to help the project reach patient groups that will promote the understanding of rare disease and communicate scientific progress and opportunities.

In summary, we believe that this more 'joined-up' approach, where data and ideas are shared between all the collaborative groups, is the best way to deliver new treatments for rare childhood neurological disorders. Our ambitious vision is that the networks we will establish, including novel therapeutic approaches, with new ways to interpret complex datasets and engage with patient groups, will benefit larger, UK-wide rare disease initiatives across all disease areas in the future.

21 Monogenic Liver Diseases - Research Node

Lead applicant: **Dr Tamir Rashid, Imperial College London**

Abstract: Monogenic Liver Diseases (MLDs) are a group of rare liver disorders characterised by a mutation in a single gene in liver cells leading to functional defects or deficiencies that results in liver damage. MLDs are individually rare but have an incidence of over 1:1000 births when grouped. MLDs typically cause severe morbidity and early death unless patients undergo liver transplantation. The improved understanding of the natural history of these diseases and the development of novel treatments can not only provide a cure but may also improve the management of the more common forms of these diseases (e.g. heterozygous carriers). Therefore, this can significantly impact the overall health and economic burden of liver disease in the UK. Unfortunately, to this date, the wider MLD research efforts have not yet been supported by a centralised body in the UK. We propose to create a unified research node for MLDs encompassing research across three centres - Imperial College London, University College London and King's College London.

Gene- and cell-based therapeutic approaches have shown great potential as therapies for MLDs. The MLD RN will aim to consolidate and synergise the existing MLD cell and gene therapy development activities.The united research endeavours will allow addressing common MLD therapy deployment challenges with respect to the delivery, safety and efficacy of these novel therapies. One of the key research blockers is lack of availability of good models for MLDs. We will establish an improved humanised mouse model with patient-specific iPSC-hepatocytes to address this challenge. This will be achieved by improving the iPSC-hepatocyte functionality and improving the liver repopulation in the FRG mouse model. The MLD RN will benefit from cross-disease collaboration with other nodes to address similar challenges. In parallel, as well as developing new therapeutics, a better understanding of the natural history of MLDs is required. The new knowledge will inform us on the patient sub-cohorts that will benefit the most from the selected therapies and the optimal treatment timing for the highest therapeutic efficacy. As such, we will initially generate national disease registries for the following MLDs: 1) progressive familial intrahepatic cholestasis, 2) alpha-1 antitrypsin deficiency, 3) Wilson disease, and subsequently we will extend this to other MLDs such as ornithine transcarbamylase deficiency, phenylketonuria and methylmalonic acidaemia. The registries will support the rare disease research community, provide increased cohesion of existing and future MLD studies, and improve the communication between the relevant stakeholders - the researchers, industrial partners, policymakers and the patients.

The MLD RN will facilitate cross-node collaboration and increase the visibility of the nodes, thus providing a better opportunity to engage with new stakeholders such as industrial partners and patient groups.

22 Rare Disease Research Platform: The renal ciliopathies national network (RCNN)

Lead applicant: **Professor John Sayer, Newcastle University**

Abstract: A group of rare inherited kidney diseases known as renal ciliopathies represent around 10% of all patients with kidney failure, who need dialysis and kidney transplants. Modern genetics and cell biology has now allowed us some important insights into this group of diseases. The most commonly seen form is called autosomal dominant polycystic kidney disease and recently the first drugs have come to the clinic to slow down this disease. Treatments that prevent or switch off the disease are still lacking. This group of patients with rare disease is relatively large with several thousand patients affected and are significant unmet challenge for our health care system. They also present a significant opportunity for innovation and investment within the UK such as we become world leaders. We believe that by aligning these patient cohorts to exploit our expertise in molecular diagnostics, deep clinical phenotyping and disease modelling we can accelerate development of novel therapeutics. The objectives of our renal ciliopathies national network (RCNN) are to: harmonise clinical, imaging and molecular genetic work-up as standard for all renal ciliopathy patients in the UK; improve genomic interpretation of underlying genetic variants and develop well characterised groups of patients who are trial ready for new personalised medicine treatments. In doing so, we aim to create a national system of support for ciliopathy patients and their families through partnerships with patient groups and charities, better interfaced with clinical care teams and researchers regardless of postal code. We believe that involving patients in these early steps of shaping the translational landscape for renal ciliopathies as we move forward will lead to better designed trials and identifying endpoints that would be meaningful for our patients.

We believe that MRC/NIHR Rare Disease investment to create the RCNN would help build strong clinical links to care teams nationally, foster successful relationships between industry and our patient advocacy groups to establish meaningful collaborations, and create the opportunity to advocate for significant industry investment to accelerate development of new treatments for the renal ciliopathies.

In summary, the RCNN aims to improve renal ciliopathy patient care nationwide, to develop infrastructure for stratified patient cohorts that are 'trial-ready' and build partnerships with academics and industry to accelerate development of much-needed translational therapies.

23 Genetics for non-monogenic rare disease

Lead applicant: **Professor Louise Wain Taylor, University of Leicester**

Abstract: Many rare diseases arise as a consequence of mutations in a specific gene or family of genes. For these diseases (termed monogenic or Mendelian disease), targeted or whole genome sequencing of patient DNA samples, together with other affected and non-affected family members, is highly effective at enabling a genetic diagnosis to guide treatment and support.

At the other end of the spectrum, common diseases are usually the consequence of interactions between environmental/lifestyle factors and genetic predisposition. For these diseases (termed non-monogenic or polygenic), determining the genetic contribution to disease risk requires large studies, usually of many thousands of cases. Understanding the genetic determinants of polygenic disease can provide insight into at-risk population and, importantly, implicate genes and biological pathways that drive the disease and thereby highlight potential new treatment opportunities.

However, there are many diseases that are non-monogenic but whose prevalence in the population is low (rare) meaning that patient DNA samples are harder to collect in large numbers. This impacts on the ability to conduct appropriate and robust genetic research for these diseases which in turn means that patients with these rare non-monogenic diseases are less likely to benefit from opportunities for new or better treatments that this type of research might enable.

The aim of this node is to address this gap in rare disease research by supporting genetic studies for rare non-monogenic disease.

24 Rare Disease Research Platform: Renal Tubular and Electrolyte Disorders Node

Lead applicant: **Dr Stephen Walsh, University College London**

Abstract: This application is for a domain called "Renal Tubular and Electrolyte Disorders". These are a large collection of very rare diseases that affect the kidney to cause problems with the salts in the blood, rather than kidney failure, although some of these diseases can do that. The diseases can be inherited or develop later in life and affect different specific cell types in the kidney. Due to their rarity, these diseases are generally poorly understood by doctors and as a result, patients often have long delays in getting a diagnosis.

Although the number of diseases in this domain is large (over 75 different diseases) and has many different causes (e.g. genetic problems, problems with the immune system, rare cancers or toxins or medicines), they are similar in important ways. Firstly, they all affect the balance of salts in the blood in some way, which means that they can be detected by routine laboratory blood tests. Second, the specific cells that are affected are all found in and can be cultured from the urine. Finally, because (with genetic diseases especially) specific types of cell are affected in each disease, they are very promising targets for genetic therapy.

Taking advantage of these similarities, we will use this funding to benefit all these very rare diseases by developing infrastructure and new technologies that can be used across the domain.

Aims:

1) Use advances in data science to scan large databases of laboratory blood tests to identify patients and make a final diagnosis early.

2) Create a pipeline to develop new gene therapies for the genetic diseases in this domain.

3) Develop a technology where we can grow specific cells from a patient's urine to make a kidney segment in the laboratory. This will allow us to test reactions to drugs and toxins before treating the patient as well as helping to make diagnoses in patients with new diseases and to help understand known diseases better.

4) To educate and train a new generation of doctors and scientists in these rare and difficult to understand diseases.

5) To bring together patients, doctors, scientists, charities, businesses, and government bodies to identify problems and solutions that face the domain.

To do this, we will work with different groups:

-Researchers in our domain. Within our universities and nationally funded laboratories, we will engage with laboratory and non-laboratory researchers.

-Industry. We aim to develop new technologies and bring them into medical practice, getting medical industry businesses involved from the start is very important.

-Other nodes in the platform that deal with different diseases will have approaches and ideas that can be used in our domain, and visa-versa.

-Clinical trainees and students. This is crucial, we need to mentor clinicians and scientists to build medical and scientific expertise and to help raise awareness of the domain in the wider medical and scientific community

-UK Medical community. By education/training, but also by more traditional means e.g. guideline documents, clinical meetings

-NHS commissioners. Ongoing NHS support for the diseases in this domain is very important.

-Patients. Who have the lived experience of both disease and the medical system for shaping future research

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-Charities. Charities already organise patients and other important groups (e.g. families, industry, researchers) and are excellent venues for networking with these groups. They also supply potential funding opportunities to support education and training.

This domain has a few specific research challenges. The large number of diseases in the domain and their rarity means that few attract any funding and research that arises is usually piecemeal and specific, and so often doesn't help other diseases in the domain, even if they are closely related. This funding really gives us a strategic opportunity to develop ways to help all the domain's diseases, and hopefully diseases in other domains too.

25 Inherited Cardiac Conditions (ICC) node

Lead applicant: **Dr James Ware, Imperial College London**

Abstract: Inherited Cardiac Conditions (ICCs) represent a challenging health burden, with a combined prevalence of ~1/200, including the commonest causes of sudden death in young adults and the leading causes of heart transplantation. In addition to their impact on affected individuals, they create a substantial burden for family members who may be at risk, and for health systems that provide long-term surveillance to both affected and unaffected relatives.

Opportunities for research using healthcare data generated as part of routine patient care could transform the diagnosis and treatment of people with these medically important conditions. However, innovative solutions are needed to overcome existing challenges around data access and linkage - and the MRC ICC node will develop these. Importantly, these solutions will also benefit people with other rare diseases, since many of the challenges faced in ICCs are shared with other conditions.

Patients with ICCs report research participation as rewarding and empowering, yet many do not access research opportunities. The MRC ICC node will remove barriers to research participation, streamlining consent processes to make routine health care data available for research, to enable recontact of potential research participants, and to build ongoing relationships with ICC patients as research partners.

The NHS Genomic Medicine Service provides remarkable opportunities for scalable research. For example, a national network of ICC centres converge on just four laboratories that provide genetic testing services to England and Wales, providing an opportunity to obtain consent and capture data at national scale through very focused investment. Many of the most pressing challenges in ICCs could be addressed using the rich repositories of data that already exist but are currently siloed. National data science infrastructure could hold and process these data and present new clinical and research opportunities. The MRC ICC node will provide the final connections to unlock these opportunities - developing robust dynamic consent procedures for data use, and linking key national data science infrastructure including the British Heart Foundation Data Science Centre (at Health Data Research UK), the National Genome Research Library (at Genomics England), and National Disease Registration Service (at NHS Digital). Governance challenges will be addressed centrally, freeing individual research groups from the challenges of linking diverse health data sources, and a new Trusted Research Environment for rare heart diseases (FREDA) will provide secure access to rich data for approved bona fide researchers.

26 Data sharing from under-represented clinical and research genomic datasets to improve variant interpretation in rare disease (RD-SHARE)

Lead applicant: **Professor Caroline Wright, University of Exeter**

Abstract: Every person has lots of differences in their DNA sequence compared with others. We call these differences genetic variants. Most variants are benign and underlie human individuality, while others may cause genetic disease. Understanding which genetic variants are benign and which cause disease is an ongoing challenge. This is particularly important for patients with a rare genetic disease, about which very little may be known. It can be very helpful to know if a genetic variant has been seen before, either in a patient or a healthy individual. But this information is not always available. Technical problems and different data sharing policies can prevent genetic information from being shared between clinical and research labs, both in the UK and internationally. Additionally, most genetic data comes from Europeans, and data from other global populations is limited or even absent. This also makes it difficult to understand the clinical relevance of rare variants present in those populations.

Our project, called 'RD-SHARE', aims to make it easier for clinical and research teams to share information about genetic variants. We will use an online platform called 'DECIPHER', which gives free access to a large interactive database of genetic variants. DECIPHER is already widely used by doctors and scientists worldwide. We will develop the new tools needed to allow the NHS to share and interpret genetic variants found in patients. We will also share genetic variants from a range of different populations and ethnicities. Knowing if a variant is common in some ethnic groups but rare others can help decide whether it is benign or causes disease. Investigating rare diseases present in patients from certain isolated groups, such as the Amish, can also be a powerful way to identify new genetic disorders.

This project will improve genetic variant interpretation and the diagnosis of rare diseases. It will also help research teams globally to collaborate and identify new rare genetic disorders. The project team includes genetics experts from key partners in academia, industry, and NHS associations involved in genetic policy and practices. Together, our work will improve diagnoses for patients, accelerate rare disease research, and address genetic healthcare inequalities for under-represented communities.

27 Establishing a National Platform for the Development of Nucleic Acid Therapy for Rare Disease

Lead applicant: **Dr Haiyan Zhou, University College London**

Abstract: Nucleic acid therapeutics (NATs) offer great potential to treat rare diseases (RDs) by addressing the genetic cause in a target-specific manner. Our Node members have strong track records pioneering both pre-clinical development and clinical trials of NATs for a diverse range of genetic disorders. To promote the development of NATs as a novel class of disease modifying therapeutics for RD patients in the UK, we propose a Node application entitled 'Establishing a National Platform on Nucleic Acid Therapy for Rare Disease' (NAT Node).

The aim of this NAT Node is to bring together relevant stakeholders, comprising of scientists, clinicians, geneticists, patient advocacy organizations and charities, industries, international non-profit organizations and regulatory bodies, to establish and coordinate a national network for NAT development.

The NAT Node will focus on rare paediatric and adult-onset disorders, including multiple paediatric highly specialised services provided at the UCL Great Ormond Street Hospital, Birmingham Women's and Children's Hospital and the paediatric department at University of Cambridge, also the adult expert centres at the UCL Institute of Ophthalmology and Moorfields Eye Hospital and UCL Institute of Neurology. The Node will be focused on severe neuro-ophthalmological, neurodegenerative and neurometabolic diseases which are uniquely conducive for the development of NAT, whilst also remaining open to other disease areas as NAT technology advances and Node develops.

The Node intends to address a number of challenges that NAT development is currently encountering in the RD field within the UK, for example 1) a lack of a national infrastructure for cross-disciplinary knowledge exchange and expertise sharing between centres leading NAT preclinical and clinical development; 2) a clear path for linking patients carrying unique mutations to NAT expertise and 3) the need to have a continuous dialogue with regulators, the MHRA specifically, in order to have guidance on the regulatory path for the expediting of clinical translation of NATs in RD.

To tackle these challenges, the Node will create several networking opportunities including: 1) scientific symposia to promote cross-disciplinary knowledge exchange between researchers, clinical and industry stakeholders; 2) open days and webinars for patient advocacy groups, charities and researchers to promote public engagement; 3) training schemes to educate and equip the next generation of scientists and clinicians with the knowledge and skills to lead future NAT research programs.

The Node also encompasses three complementary work packages during the course of 3 years, to address the overall objectives and crucial bottlenecks. These work packages focus on 1) NAT strategy design and pre-clinical development; 2) NAT scale up synthesis and pilot toxicology studies; 3) NAT clinical trial design and regulatory approval. We expect a robust framework to enable the efficient access to NAT for all the RD centres in the UK, and a clear guidance on clinical trial and regulatory to streamline the entire process of the clinical translation of NAT in RD.

The NAT Node will be led by investigators and collaborators from UCL institute of Child Health, UCL Institute of Ophthalmology, UCL Institute of Neurology, Great Ormond Street Hospital, Moorfields Eye Hospital, UKRI NATA (Oxford) and colleagues from Cambridge and Birmingham. Node members will work in partnership with Genomics England, NIHR GOSH BRC and NIHR Moorfields BRC, IONIS Pharmaceutical, n-Lorem (USA), patient advocacy groups and charities in different disease areas, UK MHRA, and the international consortia on NAT in RD such as 1M1M (EU), N-of-1 Collaborative (USA). We are determined to establish a national framework to accelerate and maximise the opportunities NATs offer for the RD patient community within the UK and beyond.

28 HistioNode

Lead applicant: **Professor Matthew Collin, Newcastle; Mark Bishton, Nottingham**

Abstract:

Domain: The domain of HistioNode is the histiocytic disorders. These comprise the histiocytic neoplasms, a rare group of inflammatory multisystem disorders, and Haemophagocytic Lymphohistiocytosis (HLH), a life-threatening hyperinflammatory state with multiple triggers. All histiocytic disorders involve pathologically activated macrophages, have a strong genetic aetiology and are potentially fatal. They are inherently linked to other rare diseases by the multi-system nature of histiocytic neoplasms and manifold triggers of HLH.

Vision: The vision of HistioNode is to improve the recognition and treatment of histiocytic disorders. To achieve this, we will develop critical infrastructure to ensure that we have samples and data for research. We will invest in biobanking to ensure that well-annotated patients samples flow from clinical networks to the UK Histiocytosis Registry, a REC-approved Research Tissue Bank. We will also forge collaboration with NHS digital, to ensure that we capture accurate incidence, comorbidity and survival data. The members of the team already form a strong clinical network across the country, through chairing two national groups, the Histiocytosis Advisory Panel (for histiocytic neoplasms) and the National HLH MDT. These structures are also supported by founder/leadership roles in the Hyperinflammation and HLH across speciality collaboration (HiHASC), National Disease Registration Service (NDRS), National Cancer Registration and Analysis Service (NCRAS), UK Histiocytosis Registry (UKHR), and NIHR BioResource for Histiocytic Disorders. As part of the MRC Rare Disease Node, direct funding and NIHR Portfolio status will significantly increase the capacity of these clinical and registry structures to recruit samples to be used in our enabling research projects.