Birmingham Health Partners Rare Disease Capabilities Outline

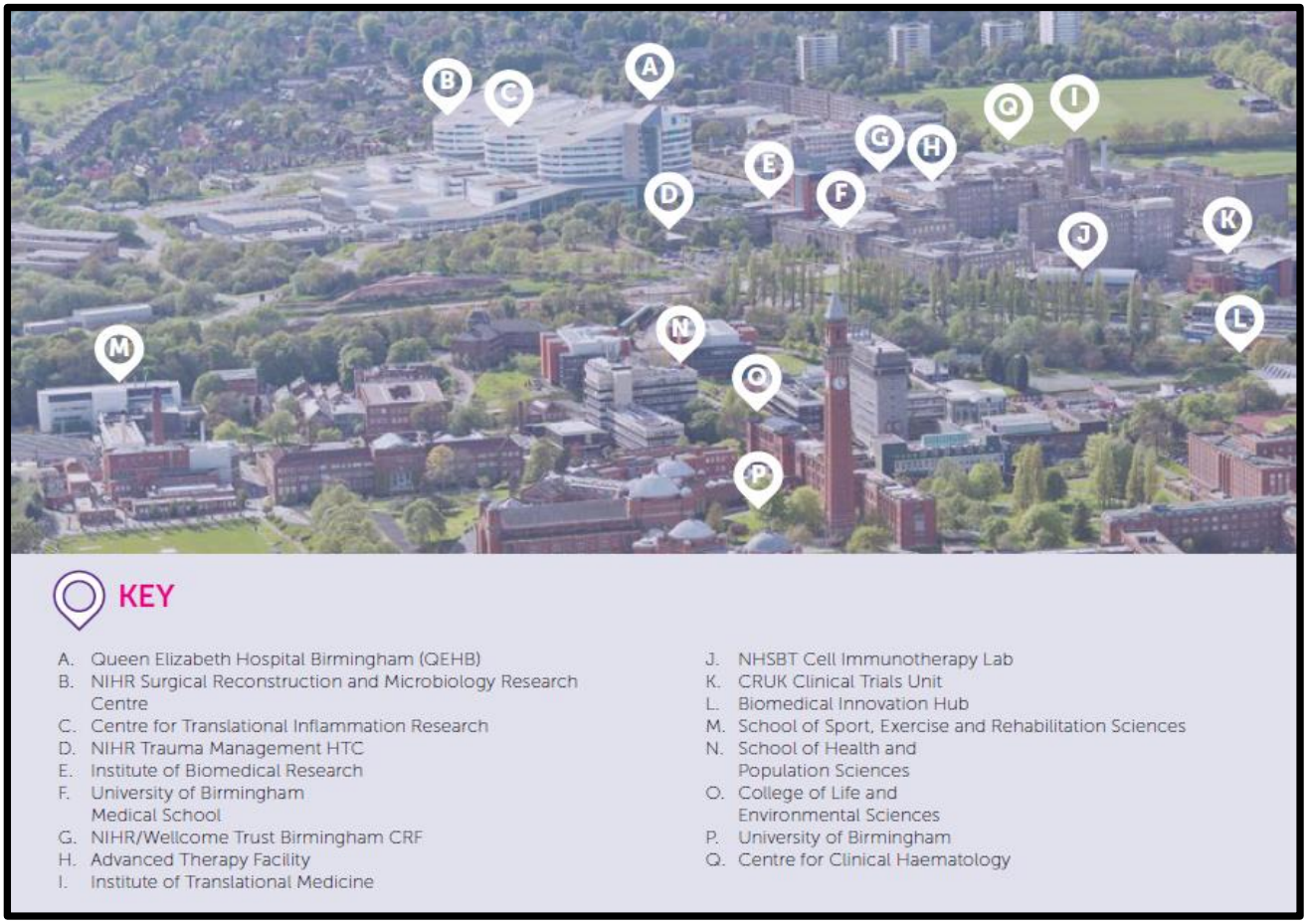
January 2017

Rare Disease Research Areas and Infrastructure in Birmingham

Birmingham Health Partners Capabilities Outline

Birmingham Health Partners

Birmingham Health Partners (BHP) is a strategic alliance between three major teaching hospitals: University Hospitals Birmingham NHS Foundation Trust (UHB, a Shelford Group hospital), Birmingham Children's Hospital (BCH), Birmingham Women's Hospital (BWH) and the University of Birmingham (UoB, a leading Russell Group university). Apart from BCH, all the partners are located on the Edgbaston campus within a 10-minute walk of each other. This vibrant and collaborative health science community is one of the largest healthcare campuses in the UK.



At BHP, discoveries arising from multidisciplinary research programmes spanning bio-engineering, physical sciences and Life Sciences can be rapidly translated into clinical benefit through a comprehensive translational infrastructure. This includes clinical trials expertise, with the largest trials portfolio in Europe, a state of the art Gene & Cell Therapy Facility and Human Biorepository, the NIHR/Wellcome Trust Clinical Research Facility (NIHR/WT CRF) which incorporates both paediatric and adult studies; and the UK's largest regional genetics diagnostic service and the West Midlands Genomic Medicine Centre. The co-location is further enhanced by UHB's clinical digital systems which are integrated with the UoB's Centre for Computational Biology to facilitate granular level informatics and comprehensively stratified patient cohorts. There is further rare disease clinical trial capacity in the Cancer Research UK Clinical Trials Unit (CRUK CTU) led by Billingham, and based at UoB. The CRUK CTU has current clinical trials in rare diseases including children, and meets the MHRA requirements to lead early phase including first man studies.

Precision Medicine

Birmingham is well placed to deliver the emerging precision medicine national strategy. BHP is a national centre for the 100,000 Genomes Project which aims to improve the prediction and prevention of disease – particularly focused on rare disease and cancer – enable new and more precise diagnostic tests, and allow personalisation of drugs and other treatments to specific genetic variants. The BHP campus is ideally placed to facilitate and undertake this testing given its access to clinical cohorts underpinned by extensive biobanking capability and innovative NHS accredited pathology services, world-leading testing methodology expertise and sophisticated clinical informatics systems across primary and secondary care. The new MRC-funded stratified medicine, deep immuno-phenotyping facility in the Institute of Translational Medicine (ITM), linked to the Clinical Immunology Service in the Medical School and the Birmingham Phenome Centre, allows novel diagnostic approaches to be tested in defined patient cohorts and adopted at speed and scale into clinical practice. Our Centre for Computational Biology is also actively developing a semantic infrastructure to enable the seamless integration of patient and biomedical related data across clinical care environments and research settings, driving data mining and analysis for enhanced rare disease characterisation at a patient level. This will enable more effective patient stratification and the development of novel diagnostic and intervention strategies.

Research Infrastructure

Birmingham has international expertise in rare diseases, having established the UK's first dedicated Centre for Rare Diseases and Personalised Medicine in 2010 focused around a cluster of basic and clinical science researchers with their clinical counterparts who look after the cohorts of patients in our partner hospitals. Integrated with the "ageless" approach enabled by the three major NHS partners within BHP, the centre has a "bench to bedside" stratified medicine focus on underpinning fundamental research providing the basis for translational research projects (including clinical trials in rare diseases) to drive the development of specialist supra-regional clinical services for diagnosis and clinical management of rare diseases.

The NIHR/WT CRF, based at UHB and BCH, provides high-quality clinical environments for experimental medicine, complex research studies and early phase clinical trials, including a dedicated Advanced Therapy facility and the first paediatric facility in the UK at BCH. This facility has recently been re-awarded the largest NIHR CRF national allocation (£12.8M) to fund the running of the facility until 2022. Since 2001, the NIHR/WT CRF has completed over 100,300 patient visits in more than 609 studies. The satellite facility at BCH has formed the base for the Paediatric Cross Cutting theme of the NIHR Translational Research Collaboration for Rare Diseases (led by Prof. Tim Barrett), funding a PhD post to increase collection of an overgrowth cohort, as identified by NHS England for Genomic Sequencing. The NIHR Translational Research Collaboration for Rare Diseases co-ordinates rare disease cohorts for deep phenotyping for congenital hyperinsulinism, steroid resistant nephrotic syndrome, type 2 diabetes in children, ciliopathy diseases, Alström and Bardet-Biedl syndromes and the respiratory cohort Alpha 1 antitrypsin deficiency. UHB and BCH are participating research sites for the NIHR Bioresource for Rare Diseases.

Our key research areas related to rare diseases are currently:

- Childhood Type 2 Diabetes
- Genetics of Overgrowth Syndromes including Sotos and Beckwith-Wiedemann
- Ciliopathy Diseases including Alström and Bardet Biedl
- Congenital Adrenal Hyperplasia

- Infantile Cholestasis
- Ataxia Telangiectasia
- Rare Platelet Disorders
- Rare Developmental Disorders such as Prader Willi Syndrome
- Renal Disease
- Lysosomal Storage Disorders
- Genomics and Models of Rare Disease
- Prenatal Diagnosis
- Fabry's Disease
- Gaucher's Disease
- Hereditary Angioedema
- Hunter's Syndrome

NHS Partners Clinical Infrastructure

BHP has longstanding strengths in:

- The range of clinical expertise across multiple specialties to manage the care of these patients (for example.: Endocrine, Renal, Liver, Ophthalmology, Diabetes, Respiratory, Neurology, Cardiology).
- Well-established transitional care pathways between UHB and BCH.
- Clinical and health informatics platforms and capability to support the clinical management and monitoring of outcome required for these patients, and through development of MyHealth@QEHB, the ability to enable patients to "own" and contribute to the management of their care.
- Significant experience in delivering multi-disciplinary clinics for patients with rare diseases (for e.g. Bardet-Biedel: Alström; von Hippel-Lindau; Tuberous Sclerosis Complex).

Diagnostic Services

The West Midlands Regional Genetics Service (WMRGS), sited at Birmingham Women's Hospital, is the largest clinical and laboratory genetics service in the UK (with more than 12,000 yearly patient referrals to the clinical service) and provides comprehensive integrated cytogenetic and molecular genetic services, including both germline genetics and somatic cancer genomics (50,000 samples a year). The WMRGS clinical team currently provides services and outreach clinics across the West Midlands region, working collaboratively with local clinicians. The service has access to multiple automated systems for DNA and RNA extraction including QIA symphony, QIA cubes, EZ1 and Promega Maxwell. Extraction quantity and quality is assessed appropriate to the purpose using one or more of Nanodrop, Picogreen quantification by Fluoroskan or Beckmann Coulter DTX880, Cubit high sensitivity analysis, TapeStation, Kappa Biosystems Library Quantification, Illumina TruSight Quality Control Primer set and an adaption of the latter for whole genome sequencing (as a Genomics England local biorepository). The laboratory has a wide range of equipment and significant NGS capacity through multiple Ilumina MiSegs and HiSegs. Extracted DNA is routinely used to provide clinical services (rare diseases, haemato-oncology, solid tumours). It has been used by other external laboratories (e.g. through UKGTN and sample exchanges between CRUK Technology Hubs); and by other external laboratory and industrial collaborators (Illumina, Oxford Gene Technology, national trials). All processes are supported by comprehensive, integrated IT platforms.

Clinical Services

BCH is a designated national principal treatment centre for paediatric cancer and leukaemia, treating 15% of UK cancer patients, and is the national co-ordinating centre for paediatric cancer trials. BCH provides eight nationally commissioned services including cranio-facial surgery, Alström, Bardet-Biedl and Wolfram syndromes, epidermolysis bullosa, retinoblastoma, complex osteogenesis imperfecta and liver disease treatment.
UHB provides nationally commissioned services including Alström, Bardet-Biedl and Wolfram syndromes, Tuberous Sclerosis Complex, heart and lung transplant, liver transplant and lysosomal storage diseases (including enzyme replacement therapy).
BCH and UHB clinicians lead specified National Rare Disease Groups: Hulton leads primary hyperoxaluria, cystinosis, salt wasting alkalosis, Kerecuk leads autosomal recessive polycystic kidney disease and Barrett leads Alström, Bardet-Biedl, Wolfram and Prader-Willi syndromes. Barrett leads in addition, an international EU-funded rare diseases registry for Wolfram, Alström and Bardet- Biedl syndromes (EUROWABB), while Hiwot leads an EU-funded Niemann Pick Disease registry. Vijay and Santra lead Gaucher's Disease, Fabry's Disease and Hunter's Syndrome, and they are also leads for the national cohorts for children with these conditions.
BCH (Kerechuk) is currently in the process of developing a bespoke clinic with the charity SWAN UK (Syndromes Without A Name).
Clinical Genetics services at Birmingham Women's Hospital, have long established collaborative working relationships with speciality groups at BCH and UHB.

Clinical Infrastructure – Translating research into excellence in care

The research strengths in Birmingham around rare diseases are intimately tied in with the development of clinical infrastructure and services. Importantly, our research pipeline has strongly fed into these services enabled by the provision of a consortium of basic and translational scientists and clinicians to take rare diseases from gene identification through to discovery of therapeutic targets and on to early phase clinical trials. Examples of this include: the national genetic diagnostic testing service for Wolfram and Alström syndromes, facilitated by the characterisation of the genes for these conditions by Prof Barrett's team. These tests are offered through the West Midlands Regional Genetics Laboratory, which has now become the national reference center for genetic testing for these two diseases, with both tests adopted by the UK NHS Diagnostic Testing Network (UKGTN). Another success has been Taylor's involvement in the discovery of the Ataxia Telangiectasia gene, through to new diagnostics and screening and creation of a highly specialized NHS England service.

Current BHP collaboration in rare diseases is being built on through the recently opened Centre for Rare Diseases (CfRD) in the Institute of Translational Medicine (ITM). The CfRD provides clinical care to adult patients on the UHB site and paediatric patients on the BCH site. The CfRD is a (Supra) Regional integrated multi-specialty, multi-disciplinary center of excellence for care of patients with Rare Diseases. Clinical care provision in the CfRD is characterized by multidisciplinary and multi-speciality rare disease clinics which focus on co-ordination of care ("one-stop" approach which integrates diagnostic testing with clinical review); provision of valuable peer support; improving access to research and information on available treatments, for patients and families affected by rare diseases.

The CfRD, and its approach to delivery of care, has been developed in close collaboration with patient representative groups for rare diseases, who have helped us to identify specifications for the patient environment, as well as helping us to understand what works best for patients in both the adult and paediatric settings. Our initiatives to work with patient groups in developing services

were highlighted in the UK Rare Disease Strategy and will feature in the first annual report on progress against delivery of this.

Patient and family care in the CfRD is further supported by:

- Dedicated patient care co-ordinators to ensure all interactions between the patients, carers and clinical service providers is seamlessly organised. This involves ensuring all required specialist staff and equipment are in place for a clinical visit, co-ordinating appointments for imaging ensuring that follow-up visits are arranged, and ensuring that clinical and other support staff at the patient's "home" base are communicated with.
- A therapeutic clinical environment focused on the specific needs of this patient group, for example provision of dedicated space to rest and eat between appointments on the days on which patients are on site for multi-disciplinary review; provision of dedicated space with social / IT media infrastructure for patient representative groups to meet; provision of dedicated space for education and training (patients, carers, clinical staff) to take place.
- A clinical informatics platform which enables highly characterised patient cohort data collection across bioinformatics (e.g. genetics, phenotyping, metabolomics): clinical informatics (e.g. diagnostic categories, co-morbidities, social phenotyping, haematology, biochemistry, drug treatments,) and health informatics (e.g. patient outcomes, patient reported outcome measures).
- IT platforms that enable patient data-sharing with other NHS organisations who may be involved in the care of these patients.
- A group of rare disease nurse specialists, a number of whom have dual adult and paediatric registered nurse status, and/or clinical genetics specialist competencies.
- At BCH, dedicated rare disease and genetic nurses provided by the Roald Dahl Marvelous Children's Charity.

The CfRD has an active development strategy in progress to expand its range of highly characterized patient cohorts through development of bespoke clinics and provision of dedicated registries and comprehensive bio-banking.

Appendix 1- Equipment Present at the Centre for Rare Diseases in the ITM beyond standard equipment

- Spirometer
- Ambulatory BP Machines
- Bio Impendence Scales
- Fibroscan
- Hitachi Aloka Nobulus Ultrasound
- ECG Machine
- Philips ie33 ECHO Machine
- ITM Research Pharmacy and Dispensing Robot
- Lab/ Sample
    - Centrifuge (non chilled)
    - Centrifuge (chilled)
    - Freezer -80 freezer
    - Freezer -20 freezer
    - Fridge –
- Dental Room
    - Dental Chair
- Ophthalmology Tech Room
    - Ophthalmology OCT (Optical Coherence Tomography) imager
    - Ophthalmology Humphrey visual field analyser.
    - Ophthalmology Multi-focal ERG
- Ophthalmology Consultant Room
    - Ophthalmology Slit-lamp

Appendix 2 – Current/previously open to recruitment **Studies** and **Registries** at the Centre for Rare Diseases

- Fabry Outcome Survey
- MPS VI surveillance programme
- **International Niemann-Pick Disease Registry**
- Qualitative interviews in Fabry disease
- Gaucherite stratified medicine project
- Alstrom interventional clinical trial
- Birdshot registry and database
- Domino study
- **EUROWABB** Registry
- **RaDar** Registry (National Registry of Rare Kidney Diseases involved in the diagnosis of the rare diseases Hyperoxaluria, Cystinosis and Cystinuria among others)
- Raptor (Cystaemine Bitarterate) study
- Tryosinaemia Study
- Proposed Liver App Project
- Acoustic Neuroma Study

Appendix 3 – Clinics currently open at the Centre for Rare Diseases in the ITM

	Clinic Name	**Specialty**	
1.	Sjogren's New	Rheumatology (1)	
	Sjogren's Follow Up	Rheumatology	
	Scleroderma	Rheumatology	11.1.17 confirmed
2.	HCM New	Cardiology (2)	
	HCM Follow Up	Cardiology	
	HCM New	Cardiology	
	HCM Follow Up	Cardiology	
3.	HCM Genetics	Cardiology Genetics (3)	
4.	Aortopathies	Cardiology	
5.	Ion Channel New	Neurology (4)	
6.	Metabolic Muscle Disorders New	Neurology	
7.	Neurogenetic Disorders	Neurology	
8.	Wolfram	Neurology	
9.	Neuro-Immunology	Neurology	
10.	Punctuate Inner Chorioretinopathy	Ophthalmology (5)	
11.	Birdshot Chorioretinopathy	Ophthalmology	
12.	Serpiginious Uveitis	Ophthalmology	
13.	HCQ Monitoring New	Ophthalmology	
	HCQ Monitoring Follow Up	Ophthalmology	
14.	White Dot Syndrome	Ophthalmology	
15	Idiopathic intracranial hypertension (new)	Ophthalmology/Neurology	
	Idiopathic intracranial hypertension (follow up)	Ophthalmology/Neurology	
16.	Development Eye Anomalies	Ophthalmology	
17.	Liver Transition New	Hepatology (6)	
	Liver Transition Follow Up	Hepatology	
18.	Wilsons Follow Up	Hepatology	
	Wilson New	Hepatology	
19.	Liver Metabolic (new)	Hepatology	
	Liver Metabolic (follow up)	Hepatology	
20.	Joint Liver and Renal	Hepatorenal	
21.	PSC	Hepatology	
22.	Non Cirrhotic Portal Hypertension	Hepatology	
23.	Neuroendocrine Tumours	Hepatology	
24.	Porphyria	Hepatology	
25.	Amyloid	Hepatology	
26.	Cystic Fibrosis	Hepatology	
	Primary Biliary Cirrhosis/Auto-Immune Hepatitis	Hepatology	6.7.17 provisional

27.	BBS. Code includes ad hoc BBS one stop/transition clinic	Nephrology (7)	
28.	Renal Genetic	Nephrology	
29.	Renal Genetic nurse led	Nephrology	
30.	Cystinosis - one stop	Nephrology	
31.	Renal Metabolic	Nephrology	
32.	Nurse Led Renal Metabolic	Nephrology	
33.	Transition (post tx - local)	Nephrology	
34.	Young Persons Joint BCH clinic - transition (post tx)	Nephrology	
35.	Young Adults SLE/Nephritis	Nephrology	
36.	Lupus	Nephrology	
37.	General IMD Clinic	IMD (8)	
38.	PKU Clinic	IMD	
39.	PKU all day clinic follow up (doctor)	IMD	
	PKU All day clinic follow up (nurse)	IMD	
40.	Joint IMD and Ophthalmology Eye Clinic	IMD	
41.	ALSTROM Test day	IMD	
42.	ALSTROM clinic	IMD	
43.	Lysosomal Storage Disorders (joint)	IMD	
	Lysosomal Storage Disorders (joint)	IMD	
44.	IMD transition (new)	IMD	
	IMD Transition (follow up)	IMD	
45.	IMD Nurse Led	IMD	
46.	IMD Psychology	IMD	
47.	Fabry's	IMD	
48.	NF2 (new)	ENT (9)	
	NF2 (follow up)	ENT	
	NF2 (New)	ENT	
	NF2 (Follow up)	ENT	
49.	Hereditary paranganglimas (new)	ENT	
	Hereditary parangliomas (follow up)	ENT	
	Hereditary parangliomas (follow up)	ENT	
	Hereditary paranganglimas (new)	ENT	
50.	Acoustic Neuroma (new)	ENT	
	Acoustic Neuroma (follow up)	ENT	
	Acoustic Neuroma (new)	ENT	
	Acoustic Neuroma (follow up)	ENT	
	Acoustic Neuroma (new)	ENT	
	Acoustic Neuroma (follow up)	ENT	
51.	Hereditary parangliomas (new)- runs alongside ENT HP	Endocrine (10)	
	Hereditary parangliomas (follow up) - runs alongside ENT HP	Endocrine	
52.	Alpha 1 antitrypsin deficiency	Respiratory (11)	
53.	Severe Asthma	Respiratory	

54.	Cutaneous Lymphoma	Dermatology (12)	
55.	Cutaneous Lymphoma	Haematology (13)	
56.	Cutaneous Lymphoma	Oncology (14)	
57.	Intestinal Failure	Gastro/Nutrition (15)	
58.	Pouchitis	Gastroenterology	
59.	PSC/IBD	Gastroenterology	
60.	Peripheral Vascular Anomalies	Plastics/Radiology (16/17)	
61.	Tuberous Sclerosis	Nephrology	
	Vulval Dermatology	Dermatology	26.2.17 provisional
	Neurometabolic	IMD/Neurology	Pending discussion
	Neuromuscular with cardiac involvement	Neurology/Cardiology	Pending discussion
	CHARGE (Adult)	Endocrinology	Pending discussion
	Research Clinics		
	DS7 - RIISC clinic	Nephrology	
	IT02 - Renal biopsy cohort	Nephrology	
	Rugby Concussion	Neurology	

As of 28.12.16

Number of clinics started in CfRD	**Number of specialities**
61	**17**
1	with confirmed start date
2	with provisional start dates
3	Pending discussions
	61 in place by end 2016
	Phase III - 6 applications

Appendix 4 –Centre for Rare Diseases in the ITM Floor Plan