

BIMDG Bulletin

British Inherited Metabolic Diseases Group



Summer bulletin 2019

Spring / Summer update! Message from the BIMDG Chair

The year is passing quickly and the BIMDG conference in Cambridge is almost upon us. We hope to see many of you there for a varied programme including development of genetic services, gene therapy, neurological manifestations of IMD, bone health and a diverse selection of members' abstracts.

As ever, BIMDG members have been busy and this packed edition of the bulletin includes updates about the BIMDG itself, reports from the CRG, MetBioNet and the reproductive pathways workshop. Writing of the 'metabolic medication formulary' is well underway, led by Will Batten. This bulletin also includes an update on the formulary of IMD 'Foods for Special Medical Purposes' by Anne Daly. Further updates will be given at the AGM in Cambridge.

Thanks to Tim Hitchin for our new style – back to nature – bulletin cover photographs which we hope will bring a bit of cheer in a climate of political uncertainty and ever-increasing funding pressures across all services.

BIMDG change in charitable status

As of February 2019, the BIMDG has applied for status as a Charitable Incorporated Organisation (CIO) with the UK charity commission. CIOs as a legal entity were established in the 2006 Charities act, with many charitable trusts applying to convert to CIO status from March 2013.

CIO status permits the BIMDG similar legal protections to those extended to a limited company, namely; status as legal person that is capable of entering into contracts, holding land and employing staff. It also affords limited liability protection to BIMDG members and trustees so that any potential financial liabilities incurred by the BIMDG will not fall to them.

This legal alteration should not noticeably change the operation or stated aim of the BIMDG, which remains:

“To relieve, for the benefit of the public, persons suffering from inherited metabolic disease by advancing the education of professionals involved in their diagnosis, care and treatment; and to promote, for the benefit of the public, research into the treatment of inherited metabolic disease.”

[Further information about the BIMDG's charitable status](#) can be accessed via the charity commission website.

Changes to the BIMDG website

Main page:

The BIMDG website is in the process of being updated. Future BIMDG bulletins should now be available without going through the member's area, while details on how to become a BIMDG member have been added to the front page.

Research tab:

This new section of the website contains a link to a registry of all ongoing research studies and is updated approximately every 4-6 weeks. This searchable database aims to catalogue:

- Local or investigator-led studies
- Studies of the natural history or pathogenesis of disease
- Clinical trials of new treatments, medications or procedures

Guidelines:

Emergency guidelines from external providers have now been added into the adult section of the emergency guidelines area and TEMPLE guidelines (Tools Enabling Metabolic Parents Learning) have now also been added to the education section. Lysosomal storage disorder guidelines for Fabry disease, Gaucher disease, Pompe disease, MPS I and MPS II will also soon be added to a new (non-emergency) guideline area.

As BIMDG dietitians we are facing growing demands from GPs questioning the need for newer protein substitutes (GMP protein substitutes) or blocking prescriptions for low protein foods – it is not uncommon for these to be confused with gluten free products or a belief that these items are a luxury. IMD Dietitians spend significant time each week negotiating patient access to these products with either GPs, community pharmacists or prescribing dietitians.

The formulary of IMD 'Foods for Special Medical Purposes' is an ideal opportunity to provide prescribers with a comprehensive guide about the use of these products written by IMD dietitians, that has been ratified by the BIMDG. Many GP surgeries face cost pressures but fail to understand the need of IMD patients who require essential supplies of low protein foods (providing up to 50% of their energy requirements), and the need for choice with protein substitutes to enhance adherence. Hopefully the formulary will provide extensive information for GPs, pharmacists and dietitians in the community on the use of IMD 'Foods for Special Medical Purposes.'

We have a small working group of both adult and paediatric IMD dietitians now taking this forward.

MetBioNet: Metabolic Biochemistry Network. Update and review of resources

What is The Metabolic Biochemistry Network (MetBioNet)?

We are a group of specialist metabolic laboratories from the UK and Ireland, comprising 18 stakeholder and five associate laboratories.

What does MetBioNet do?

We address topical issues of concern to metabolic laboratories including the challenges of ISO15189 accreditation to specialist services and the provision of metabolic services outside normal working hours. We develop and review best practice analytical guidelines and we have a role in workforce planning. We are currently working in close collaboration with the Association for Clinical Biochemistry to develop programmes to ensure the current and future availability of appropriately trained clinical and biomedical scientists in IMD. MetBioNet also works closely with external organisations including the UK Newborn Screening Laboratory Network, the BIMDG and the Metabolic Clinical Reference Group.

What resources does MetBioNet provide?

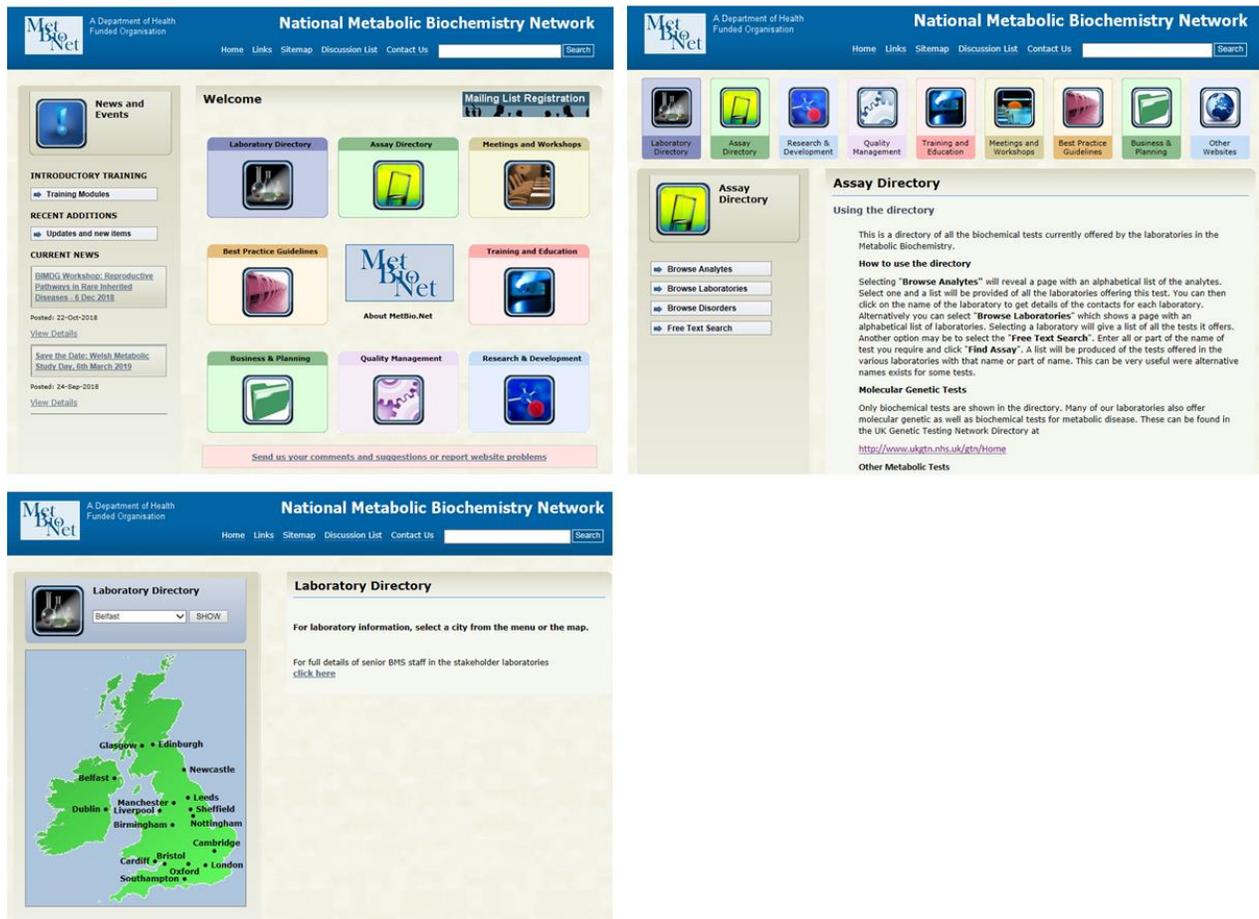
The MetBioNet website (www.metbio.net) receives over 300 visitors per day. Some pages are shown below. These include:

- **Laboratory directory:** A map of all MetBioNet laboratories is provided, with links to the laboratory postal address, contact details and accreditation status.
- **Assay directory:** A one-stop shop for all the specialist biochemical tests currently offered by MetBioNet laboratories -there are options to browse by analyte, laboratory or individual disorder.
- **Best practice guidelines:** These include investigation guidelines (e.g. hypoglycaemia, hyperammonaemia), some more specialist laboratory guidelines (e.g. lysosomal enzyme reporting) and links to guidelines from BIMDG and other relevant organisations.
- **Educational resources:** There are training case reports which offer a structured approach to the investigation and diagnosis of metabolic disease, presentations on methodology and clinical investigation of IMDs.
- **Technical resources:** For individuals working in a metabolic laboratory, there is a comprehensive chromatogram and interpretive resources library which provides advice and examples of traces from patients with known rare metabolic disorders which are often difficult to source elsewhere.

What is the benefit of being part of a network?

- **Networking:** A major strength of the group is the strong working relationships which have developed over the years providing an informal network for discussing difficult cases, interpretation of unusual findings and addressing quality and technical issues.
- **Resources:** A range of useful resources has been developed, analytical quality improvements have been delivered and training and educational needs are being addressed.

- **Working together.** By engaging with other strategic groups we have helped to influence the provision of metabolic services in the UK. This has, and will continue to be, extremely important in order for metabolic laboratories to be able to respond and adapt to the ever- changing technological and organisational landscape within the NHS.



This is an edited version of an article that appeared in *ACB News* December 2018 (*The Association for Clinical Biochemistry and Laboratory Medicine*, acb.org.uk). Article by Ann Bowron, Consultant Clinical Scientist, Newcastle upon Tyne Hospitals NHS Foundation Trust and Nicola Merrett, Consultant Clinical Scientist, University Hospital Southampton NHS Foundation Trust.

BIMDG studentships

The British Inherited Metabolic Disease Group (BIMDG) will consider supporting undergraduate students to gain valuable experience in the area of inherited metabolic disease. A stipend of £200 a week, for a maximum of 8 weeks, is available. It is anticipated that up to two studentships will be awarded each year.

Applications are invited from disciplines relevant to patients with inherited metabolic conditions. Students will need to identify a supervisor or vice versa. Potential supervisors should apply by submitting a one-page (A4) project proposal that includes background, aims and approach to be employed. A statement of how the project will benefit patients with inherited metabolic disorders should be included. A CV of the prospective student must also accompany the proposal.

Congratulations to Melissa Kuo (supervised by Prof. Shamima Rahman) and Ozlem Yilmaz (supervised by Prof. Anita Macdonald) who have been awarded BIMDG 2019 Summer Studentships for their projects 'An *in vitro* proof of principle study to test the efficacy of translational read-through therapy for mitochondrial disorders' and 'Natural protein and phenylalanine tolerance and metabolic control in patients with hereditary tyrosinaemia type I', respectively. We look forward to reading their project reports in the next edition of the bulletin.

BIMDG Travel grants

To help assist members attend conferences, meetings or workshops in the area of inherited metabolic conditions, the British Inherited Metabolic Disease Group (BIMDG) will consider travel grant applications. This is limited to a maximum of £500 pounds and is restricted to individuals who have been members of the BIMDG for 2 or more years. To apply, follow the contacts list on the BIMDG website members area and email an application to general contacts, including the name of the meeting and the cost of travel.

The metabolic clinical reference group

Robin Lachmann

The Metabolic Clinical Reference Group starts a new three year cycle this summer. Over the last months, we have appointed the new members and set out our work programme. The membership of the new CRG will be smaller. We have a chair, seven clinical members, two patient public voice (PPV) members and up to three members nominated by affiliated professional bodies (in our case the BIMDG). The seven clinical members can now come from anywhere in the country, instead of representing specific regions. After an open application process, Bernd Schwann, Germaine Pierre, Helena Kemp, Louise Simmons and Mike Champion have been reappointed and Mel McSweeney and Chong Yew Tan will be joining the CRG. Toni Mathieson and Lindsay Weaver will continue as the PPV members. Elaine Murphy and Rachel Skeath are the affiliated group members. Bobby Macfarland, Maureen Cleary, Marjorie Dixon, Suresh Vijay, Patrick Deegan, Evelyn Frank and Sara Hunt will be standing down and I would like to thank them for all their hard work over the last three years.

Going forward, our first priority will be to continue with the Metabolic Service Network Review and try and secure some tangible outcomes. We will also be reviewing the Quality Dashboard to try and make sure we are collecting useful data, and continuing to work to ensure patients can actually access the medicines which are available on the NHS. We will also continue to be involved in policy development. Any clinician can suggest a new policy for development and, if approved by NHSE, the CRG will appoint a policy working group to take the policy forward. These working groups (which may also be convened to look at things other than new policy propositions) will provide an opportunity for people who are not members of the CRG to get involved in the commissioning process and service transformation. If you have ideas on improving the services we provide, then please speak to a member of the CRG and we will try and find ways that we can take your ideas forward together.

BIMDG workshops

The BIMDG supports members to develop 1 day workshops in related areas of interest to members – clinical, laboratory, nursing, dietetic, psychological or other related groups. Up to two workshops per year (generally spring and autumn) can be supported.

Any member wishing to develop a BIMDG workshop should email a proposal to the chair (at least 4-6 months in advance of the proposed workshop). This proposal should include any estimated costs of the workshop and how it is expected these costs will be met. The BIMDG committee may also directly approach appropriate members to develop specific workshops.

Workshops should generally be aimed at no more than 50 participants and should be practical in nature with clear learning objectives or goals. Workshop details, when finalized, will be available on the website and emailed to members.

Workshop report

Mike Champion

Reproductive pathways in rare inherited diseases

The original idea for the workshop developed from discussions within the Metabolic CRG considering the current restriction of Pre-implantation Genetic Diagnosis (PGD) to couples who have no unaffected children, potentially a false economy if a couple were to have a further affected child. This led to discussions around the challenges of access and acceptability of reproductive technologies to our families. The workshop provided an update on current techniques and developing technologies in the morning with the afternoon focused on improving awareness and the challenges for different at risk groups.

Contributors:

Dr Tessa Homfray	St George's Hospital, London
Dr Rhiannon Mellis	University College London
Dr Sue Price	Northampton General Hospital
Prof Bobby McFarland	Royal Victoria Infirmary, Newcastle
Prof Sarah Salway	University of Sheffield
Naz Khan	Manchester University Foundation Trust
Alison Wilson	Belfast City Hospital, Belfast
Katrina Sarig	Jnetics
Lucy Henighan	Parent
Dr Frances Elmslie	St George's Hospital, London

Prenatal Testing

Dr Tessa Homfray gave an overview of current practice reminding the audience of the various techniques used in prenatal testing. Non-invasive methods include biochemical and genetic pre-pregnancy screening, eg maternal urinary sterols may be used to diagnose Smith-Lemli-Opitz (SLO) indicated by the increased 7-dehydropregnanetriols:pregnanetriol ratio. Private labs currently offer genetic pre-pregnancy screening for over 600 diseases; the output from which is immediately referred to the NHS for follow up without the appropriate counselling prior to testing. The gene panels contain many metabolic conditions and often there is no experience of the disease in those offering the test. It is important to look at the inheritance patterns and to remember germline mosaicism will not be detected. If there is reduction in reproductive ability due to the condition, then *de novo* mutations are more likely for dominant conditions, eg GLUT1 deficiency syndrome.

When considering invasive prenatal testing such as Chorionic Villus Sampling (CVS), amniocentesis, fetal blood sampling and other tissues, a family history is usually a pre-requisite. CVS is usually performed from 11 weeks and requires placental tissue. The risk of miscarriage is less than 1%, but is still greater than the natural rate of 1 in 500. During interpretation it is important to remember placental mosaicism and to check for maternal contamination of the sample. Amniocentesis uses fetal skin and bladder epithelial cells which need to be cultured first due to the reduced number of cells available, so that this method takes longer. Biochemical analysis of amniotic fluid is not good as maternal metabolism detoxifies many of the metabolites. Metabolism is also anaerobic *in utero* meaning some conditions, such as respiratory chain disorders, will not be evident.

Next generation sequencing (NGS) is increasingly being used, with results available in 2 weeks. Gene panels can be used to target specific conditions eg rhabdomyoma in the heart to exclude tuberous sclerosis. Another approach is to use pre-natal exome to link genome to phenotype for diagnosis.

Non-Invasive Prenatal Diagnosis (NIPD) & Fetal Exome

The development of these techniques was described by Dr Rhiannon Mellis. The presence of cell free DNA (cfDNA) in the maternal circulation is a mix of predominantly maternal cfDNA with some fetal cfDNA which is of placental origin. CfDNA was originally used for aneuploidy testing, however, an abnormal result may reflect cell lines confined to the placenta or from the mother and so invasive testing is needed to confirm the result in fetal material.

NIPD does not require invasive testing avoiding the miscarriage risk. It is not affected by placental mosaicism. The first successful use for a monogenic disorder was the detection or exclusion of paternally inherited variants for the dominant conditions: achondroplasia and thanatophoric dwarfism. The presence of the affected paternal variant is diagnostic. The advent of Next Generation Sequencing (NGS) has aided the development of NIPD for recessive disorders where the parents carry different mutations; either confirming or excluding the presence of the paternal mutation in conditions such as cystic fibrosis and beta-thalassaemia.

Definitive NIPD for recessive and X-linked disorders requires determination of the inherited maternal allele. This is achieved with Relative Haplotype Dosage Analysis (RHDA) combining relative mutation dosage (the proportions of wild type and mutant alleles in the maternal plasma) with linkage analysis to test for the haplotype linked to the mutation. The more single nucleotide polymorphisms (SNPs) included, the greater the statistical power. Interpretation may not be possible if the parents are too similar as SNPs will not be different enough, eg if the parents are consanguineous.

The majority of cases require bespoke NIPD which is labour intensive and, therefore, not easily scalable. This requires DNA from both parents and the affected child and/or other child(ren). The test is developed pre-pregnancy and offered at 9 weeks gestation and can detect fetal DNA in blood in sufficient quantities to run the maternal germline at the same time. Turnaround time is 5 days. At UCLH this has been offered for two years; 37 pregnancies tested (previously 2 per year when invasive only) indicating a desire for non-invasive testing. Advantages include that testing is early, safe and non-invasive with a rapid turnaround. Concerns include parental confusion, as this is just a blood test and there may be a pressure to test as there is a lack of risk compared with older prenatal invasive methods. This can impact on parental choice and the potential of direct to consumer testing.

Fetal whole exome screening (WES) is being developed for testing in the fetus found to have abnormalities. At present 60% of abnormal fetuses detected on ultrasound remain undiagnosed following genetic testing. Targeted clinical exomes are being explored, eg 240 genes for skeletal disorders with 6-80% reported success depending on the selection process adopted. Phenotyping is difficult prenatally as, in many conditions, the picture evolves beyond delivery. The challenges of reporting remain: which variations to report, whether to report pathogenic variants if unrelated to the phenotype, what if variant is of adult onset and what to do with variants of unknown significance?

Mitochondrial Donation

Professor Bobby McFarland gave an update in the development of the mitochondrial donation programme at Newcastle and the clinical pathway for potential mothers with a high risk for transmitting serious mtDNA disease where PGD is considered inappropriate. It is recognised that egg donation is not acceptable to everyone as the infant will not be genetically related to both parents. Prenatal testing and PGD are only suitable for women who produce eggs with lower levels of mutant mtDNA. The preferred mutant load is <30% which is considered safe level, however, in Holland <18% mutant load is the cut off. Further challenges arise for example in considering a mother with a <60% mutant load who is healthy, and determining whether or not it is justifiable not returning an embryo with a 40% load. Blastocyst morphology is also important in selection.

A 2015 Act of Parliament was passed which permitted mitochondrial donation and following four different scientific reviews, the HFEA granted a license in March 2017. It is estimated that there are approximately 2473 women at risk, equating to 150 births per year in the UK. Wellcome have funded the programme to follow up to 18 months post-delivery. The method to be used is pronuclear transfer from the fertilised zygote rather than maternal spindle transfer from the unfertilised zygote. A small amount of cytoplasm is carried over. Mitochondrial DNA analysis is performed at 5-8 days of age in blood, urine and buccal cells. This will be repeated at 18 months with up to five years active follow up.

Patient focus groups were formed to develop the care pathway. There is a separate donor pathway and consent process. The mitochondrial genome is looked at in two tissues for donors. Women are initially seen in the Mitochondrial Reproductive Advice Clinic to confirm the genetic diagnosis, assess fitness for pregnancy and explore the options available. Once assessed, if a couple wishes to use preventative IVF-based strategies, they are seen in the Mitochondrial Assisted Reproductive Technology (ART) Clinic for detailed discussions of their situation and suitability. To date, 64 have been seen in the Mitochondrial Reproductive Advice Clinic with 40 progressing to the Mitochondrial ART Clinic, with 7 going forward to PGD and 12 mitochondrial donation, with 3 actively in process at present.

PGD Policy: Sue Price

Dr Sue Price guided us through this difficult area of policy. PGD was first introduced for X-linked disorders in 1990. The embryo is cultured to the day 5 stage blastocyst stage. It is important to remember that there is a mis-diagnosis rate. PGD is linked in couples' minds to IVF and therefore the risks of IVF treatment. The complications include hyperstimulation, pelvic infection and miscarriage/ectopic pregnancy. Approximately one quarter of couples move on to undertake full treatment after meeting with the Geneticist. Success is 1 in 5 (1 in 3 will reimplant).

In 1990, special status was given to the embryo in law relating to IVF work (Human Fertilisation and Embryology Act, 1990). Challenges developing PGD included defining 'serious' conditions suitable for the technique. Disease facts include age of onset, how the individual is affected, what treatment is available and funded, the speed of progression, whether there is intellectual impairment, the impact/burden of the condition, morbidity and family factors. In the early days, the conditions referred were all serious, but discussion is becoming more difficult, more nuanced now that we are able to test for more conditions. Access to PGD remains patchy and commissioning is a 'postcode lottery'. Factors improving IVF success include BMI 19-30, female <40 years and non-smokers as parents.

The 2014 PGD policy remains the current policy prompting a timely review. There are issues defining what is a PGD cycle. Embryos are stored for up to 10 years and couples funded up to 3 cycles. The policy excludes gender selection for non-medical reasons, isolated HLA donor sibling for a child requiring an allogeneic stem cell transplant and to address infertility or miscarriage of unknown aetiology. Difficult areas include: strong opposition from religious, eugenic and disability groups, reduced penetrance conditions, eg cancer genes and intersex states, conditions with a wide range of expression, eg NF1, conditions where all offspring carry the mutation but with a variable load, eg mitochondrial, embryos selected on risk without definite mutation, eg Huntington's and the use of karyomapping which highlights aneuploidy. There are also increasing social challenges such as single adults, single sex couples, and how many transfers are allowed? Rationing treatment is becoming increasingly unpalatable. The majority of couples fund their own IVF. There is no rationing of prenatal testing.

Consanguinity

Professor Sarah Salway gave an enlightening lecture on this subject. Marrying close blood relatives is a common practise in many countries. However, since blood relatives are more likely to carry the same genetic variants than unrelated people, there is a greater risk of recessive disorders in consanguineous unions (30/1000 vs 2/1000). Recessive disorders contribute to increased infant morbidity and mortality. The risk of all congenital abnormalities is roughly doubled in populations practising consanguineous marriage, but risk clusters in families and so most are unaffected. Despite increased genetic risk to offspring, there are important social and cultural benefits. Marriage within the family strengthens family ties and supports, protects family wealth and property for future generations, preserves culture, traditions, upbringing and values.

There are a number of concerns in communities: inadequate information and confusion, ill equipped professionals to counsel them, a lack of confidence with certain communities, poor access to services and media attention of which much has been negative. What is the best way to address the genetic risk associated with consanguinity: discourage or inform and empower? A 3 stranded approach is in its infancy in the UK: family centred genetic services for at risk individuals and families, training to enhance confidence and competence of health professionals and activities at community level to raise genetic literacy and encourage uptake of services. Testing is offered by a culturally competent Genetic Counsellor who can address beliefs, supported by integrated services. It has been found engaging health professionals can be difficult and opportunities are missed to refer. Commissioning expectations may be unrealistic as cost savings do not occur rapidly and so national leadership is needed. Core themes agreed include interprofessional working, increased equity of access to information and services, cultural competence and empowering and embedded evaluation and knowledge sharing. Increasing accessibility is the key priority and the need to increase family cascading of knowledge, ensuring this remains in context. Efforts to increase genetic literacy include the sharing of resources nationally, co-designed with local communities. The next steps are to set up a national steering group, develop working groups, establish a dissemination of knowledge exchange and identifying research area priorities. What can we do as individuals? Suggestions include upskilling yourself, to ensure referral of cases to Clinical Genetics Services, advocate for equity of access and contribute to national working groups under construction.

The experience working with South Asian families in East Lancashire

Naz Khan developed these themes further describing the initiative in East Lancashire where 22% of the residents have an Asian background with an incidence of recessive disorders in childhood 12 times greater than in Caucasians. Where recorded, 95% of Asian parents with an affected child were consanguineous. 70% originate from the same region of Pakistan.

In 2003, the Department of Health funded a 2 year partnership working on a proactive family centred approach offering carrier testing for all other family members aiming to reduce barriers, facilitating information for the family and addressing beliefs such as black magic or punishment from God. The study showed that 95% of the parents of an affected child took up the genetic service offered. Only 6 siblings offered carrier testing declined. 8 prenatal tests were requested and 2 terminations requested for 2 affected pregnancies. Genetic literacy improved. Information on the condition was particularly valued. 64% were not sure of inheritance and 84% were not aware of the risk to other family members. Initiatives include tutorials for 16 to 18 year olds in college, clinics in community centres and the use of websites. Challenges include recruiting genetic counsellors with appropriate skills and HCP engagement dropped off post training. Funding challenges confirm the need for a national initiative.

Travelling Community Experience

Alison Wilson works with families from the Travelling Community which share many of these issues. There are 50,000 Travellers making up 1% of the Irish and 0.2% of the Northern Irish populations. Most families do not travel as much currently. Families are often dependent on the social welfare system for which you need to be settled. The birth rate is high and mothers are younger. Life expectancy is low, late 50's, with a high suicide rate. Literacy levels are low, but families with a medical problem tend to become more literate. There are clearly defined family groupings, or clans, with consanguineous unions being part of this culture, although there is more mixing than previously, but HCP's need to be aware of clan issues. There is a mistrust of the medical community. Medical knowledge is limited and so conditions within the family may be misreported, eg 'autism' and 'Downs' are commonly used to describe physical and intellectual disabilities. Privacy and secrecy surrounding medical issues can be problematic with a reluctance to discuss deaths, miscarriages and stillbirths. Family relationships are often inaccurately described with multiple 'aunts' and 'uncles'.

There are over 100 clustering conditions that are more common in the travelling community. An individual family may have more than one and so it is important to prepare families for testing of more than one condition and to split testing across multiple appointments to avoid confusion, concentrating on a single disorder in each appointment. Expectations tend to be high that a good/negative result equals a normal baby and so it is important to state what is not covered by the test and the risk of other conditions. Prenatal diagnosis is increasingly being sought and termination of pregnancy is becoming more acceptable. PGD is increasingly being used, but this remains taboo with older generations and so the couple may not want the family to know. Literacy issues complicate consent and so it is vital that all decisions are understood and clearly recorded.

Jewish community experience

Katrina Sarig described the Jewish community's response to the increased incidence of the 'Jewish Genetic Disorders' such as Tay Sachs. It is estimated that 1:5 in five Ashkenazi Jewish carry at least 1 of 9 conditions. 1 in 40 are BRCA positive compared to 1 in 500 in the general population. Other estimated carrier frequencies for the Ashkenazi population are: Tay Sachs 1 in 25, Canavan 1 in 40-57, GSD1a 1 in 71 and Niemann Pick 1 in 90. Arranged marriages are tested and given a code to check genetic compatibility, and a match would not continue if the screen is positive. Gene panels have evolved including Sephardic screening for a different group of conditions in the US. Increasingly private screening is being undertaken by couples.

The Jnetics Charity has screened 423 people so far with 1 in 5 carrying at least 1 disorder and 3 carrier couples detected. The Geneius programme focuses on university and 6th form students and pre-marriage couples. Over 1250 students have been to an education event with 1005 undergoing screening, 60 to 75% of the eligible group. The pre-marriage programme is undertaken through the synagogue process. A fortnightly screening clinic is held at Barnet Hospital which also offers screening at a distance with teleconference counselling and the use of saliva samples. The cost is £190 per individual (with the real cost £250). The programme is endorsed by the religious community as this is seen as a good deed (mizvah), with Jewish press acceptance and support helping increase uptake along with promotion on social media.

Patient journey

The final talk by Lucy Henighan, a mother who has undergone PGD, helped ground us all as to the realities and stresses of reproductive technologies in real families. Key messages were the anxiety and stress waiting for genetic results and the realities of the odds of having an embryo suitable for re-implantation may be much lower than the 1 in 4 affected. The multiple scans performed to assess progress were difficult wondering if the baby was going to be fine. The whole of pregnancy was a very anxious time. Navigating the NHS was generally difficult and the lack of continuity translates into re-explaining the circumstance each time. Linking up online, joining a forum was particularly helpful and provided wonderful support.

Workshop Discussion

The final discussion was led by Frances Elmslie. The importance of all HCPs in linking with families to discuss genetic issues and not missing the opportunity to refer to genetics services was emphasized. The voluntary sector is working more closely with medical services to help boost genetic literacy. It was questioned whether we should reverse the reduction in home visits and allow relatives to be brought along to the clinic. Accessing other family members without a GP referral is seen as very important. In Belfast, being helpful with other concerns such as helping with benefits cements links with medical services and builds trust.

Couples often do not consider PGD as an option as only one child is allowed. However, this area is being looked at following a current legal challenge that this is discriminating against a family with a child. It was also discussed that the first cycle is the most expensive, £15,000. Approximately 50% will have a further stored embryo available and therefore do not need all the drugs, egg collection etc, reducing the costing to approximately £1500.

Considering the next steps, the investment in technology needs to be balanced against investment on outreach and getting in to the home/community. Equipping CNSs, HCs, HVs, and GPs with basic knowledge may be a cheaper alternative to increase engagement and increase referrals to the local Genetics service. Many questions remain unanswered: how to support local screening for identified populations; what is the National Screening Committee's role; and how to deal with the challenge of private sector testing without appropriate counselling and follow up. Prof Salway is leading the New Genetics Policy and invites anyone who wishes to be involved to get in contact. The Genetic and Metabolic CRG's should work collaboratively to move the agenda forward.

Suggested Reading

- Ali PA, Salway S, Such E, Dearden A, Willox M. Enhancing health literacy through co-design: development of culturally appropriate materials on genetic risk and customary consanguineous marriage. *Prim Health Care Res Dev.* 2019;20: 1-13.
- Craven L, Murphy J, Turnbull DM, Taylor RW, Gorman GS, McFarland R. Scientific and Ethical Issues in Mitochondrial Donation. *New Bioeth.* 2018; 24:57-73
- Hayward J, Chitty LS. Beyond screening for chromosomal abnormalities: Advances in non-invasive diagnosis of single gene disorders and fetal exome sequencing. *Semin Fetal Neonatal Med.* 2018;23:94-101
- Khan N, Kerr G, Kingston H. Community engagement and education: addressing the needs of South Asian families with genetic disorders. *J Community Genet.* 2016; 7: 317-323

Conference report

Greg Toulson

Inherited metabolic disease from bench to bedside & back again - Institute of Child Health 10/05/2019

Professor Simon Heales and Professor Sara Mole hosted this one-day showcase of the newly established metabolic disease network between Great Ormond Street Hospital, the Institute of Child Health, University College London Hospitals and the National Hospital for Neurology and Neurosurgery. The morning session was used to give an overview of the current Inherited Metabolic Disease (IMD) services available within the London network and the afternoon used to present a broad range of current and emerging research topics within the field of metabolic disease.

The first talk of the day was by Dr Amanda Lam on the mitochondrial disease laboratory service provided at Queen Square. This service receives around 300 muscle biopsies per year and provides functional assessment of mitochondrial respiratory chain enzymes which, despite the growing role of genetics in diagnosis, is an essential capability given the frequently complex or inconclusive genetics that can often be seen in mitochondrial disorders.

Dr Lam described the recent case of a 6-hour old neonate that presented with profound multiple organ dysfunction and a plasma lactate of 19.4 that was subsequently investigated for mitochondrial disease and found to have decreased total CoQ₁₀ and deficient complex II-III activity, indicative of CoEnzyme Q₁₀ deficiency. Shifting to ongoing research and development within their laboratory, Dr Lam presented data on FGF-21 a promising marker of mitochondrial stress and concluded with a brief mention of their laboratories interest in respiratory chain super-complexes.

Dr Simon Pope then gave a brief description of the neurotransmitter service, highlighting that unlike many neurological disorders the dopamine and serotonin pathway disorders are often highly treatable. Dr Pope shared a video of an infant with profound hypotonia, head-lag on lifting and a thrusting tongue; following lumbar puncture and analysis, the child was found to have a reduced CSF homovanillic acid and MHPG levels indicating tyrosine hydroxylase deficiency. Upon treatment with L-Dopa, the infant's tone and overall cognitive function were dramatically improved.

My personal take home message of the talk was that there are effective rostrocaudal concentration gradients of monoamine metabolites down the spinal cerebrospinal fluid column and as such, samples taken for CSF neurotransmitters need to be taken in the correct draw order (not just into the correct containers with/without inhibitor).

Derek Buke, manager of GOSH's enzyme laboratory, discussed their role in the diagnosis and monitoring of lysosomal storage disorders. As with other talks of the day, new LC-MS methods are changing and expanding their service. As enzyme replacement therapy (ERT) for lysosomal storage disorders enters routine clinical practice it has pressed the need for developing quantitative biomarkers by which to aid in judging ERT efficacy on individual patients. This is now the case with MPS-IV, where a quantitative LC-MS method to measure keratan sulphate has now been put into routine service, and in Fabry disease where Gb3 and lyso-Gb3 can be used.

Derek went on to discuss how the development of these high sensitivity, quantitative LC-MS methods in conjunction with next generation sequencing have shown that lysosomal dysfunction is apparent in some patients with Parkinson's disease and Dementia with Lewy bodies. As such, the conception of lysosomal storage disorders may well change in the future to encompass a proportion of patients with these late-in-life conditions.

Dr. Ralph Wigley discussed the glycogen storage disorders enzyme laboratory service at Great Ormond Street. Unusually for an enzyme service, they have managed to move to a more automated workflow for their service, improving assay consistency and sample throughput. Although genetic testing for GSD's has now moved from a confirmatory second-tier investigation to a front-line investigation, enzyme functional testing is still essential, especially where the interpretation of variants of unknown significance is required.

Helen Prunty outlined the role of metabolic biochemistry in routine clinical practice, exemplified in a presentation of an adolescent male who was admitted with reduced consciousness and seizures. Biochemistry showed an ammonia >1000 with no metabolic acidosis. Plasma amino acids showed a reduced citrulline, and urine organic acids the presence of orotic acid and uracil. As such, a diagnosis of ornithine transcarbamylase deficiency (OTC) was made, a rare finding in a male of this age.

Simon Heales closed the morning session by summarising some of the benefits of the London based clinical/research metabolic network. Among these is a translational research mass-spectrometry group with the intent of strengthening the pipeline between basic research identifying a new biomarker and its deployment into clinical practice. Recent and ongoing developments include LC-MS methods for keratan sulphate, quantitative glycosaminoglycan analysis; multiplex enzyme assays measured by MS; a rapid, out-of-hours service for plasma amino acids; and Glc4 for the diagnosis and monitoring of Pompe disease. Moving into developing treatments, Simon concluded with data showing decanoic acid to be a key mediator in the benefits of ketogenic diet.

The plenary Otto Wolf lecture was given by Professor Sir Doug Turnbull on the history and recent developments in mitochondrial disease in the UK. Professor Turnbull was integral in the establishment of the national mitochondrial disease service in 2007, a collaborative network between Newcastle, Oxford and Queen Square, London. This service requires a highly multi-disciplinary approach for the diagnosis and management of patients given that they may present at almost any age and with dysfunction of almost any organ.

To illustrate the diversity of symptoms seen in mitochondrial disease, ranging from the subtle to the life threateningly profound, Prof. Turnbull showed a video of a patient with barely perceptible hand movement signs signifying a focal seizure. Upon MRI the patient showed florid cerebral oedema and severe focal lesions. A second patient showed almost no outward clinical signs; however, an ECG trace showed almost complete heart block.

Treatments for mitochondrial disorders are sadly limited to managing their myriad of symptoms; neither slowing nor curing the underlying disease. Yet for the first time, women with mitochondrial disorders have the potential future choice of being able to bear children that are unaffected by their condition. This development is due to groundbreaking work being led by Professor Turnbull's Newcastle group using pro-nuclear transfer (PNT). This technology allows parents to conceive via IVF; the fusing pronuclei inside the developing zygote are transferred into an oocyte of an unaffected donor, thereby only keeping the donor supply of (unaffected) mitochondria. PNT is currently being assessed as part of an 18 month clinical trial based in Newcastle.

Seeing an embryologists-eye-view video of this PNT process was both fascinating and profound. That a human cell nucleus can (at least at this early stage) be completely removed, transferred into a completely different cell and then rebooted seems the stuff of science fiction.

Dr Emma Clements talk, mainstreaming genomic medicine, reflected upon how the NHS is currently on the cusp of being able to offer whole-exome and whole-genome sequencing as a routine investigation. Exemplifying the difficulty in sifting through all the information this produces, Emma stated that within any healthy individual's genome there are around 10,000 protein altering variants, 100 protein truncating variants and around 60 variants of unknown significance (VUS). Against this background a clinical geneticist must then identify potentially pathogenic variants, especially difficult for intermediate (class-3) variants. To empower this transition, Emma discussed the national genetics laboratory reconfiguration, establishing standardised SOPs, the proliferation of new bioinformatics tools and a soon to be launched national genomic test directory. To conclude, Emma discussed Rapid Paediatric Sequencing (RaPS), a rapid next generation sequencing workflow whereby critically ill children could be given a genetic diagnosis within the first 5 days of life.

Dr Wendy Heywood's presentation, bringing Omics to the clinic, fleshed out their group's role in enhancing the pipeline between biomarker discovery and actual deployment into clinical practice. Wendy characterised the "Valley of death" whereby potential new biomarkers fail when transitioning through the retrospective validation stage and into the clinical assay development stage, an area where they particularly focus their efforts. This approach has enabled them to relatively quickly validate and soon roll-out a new lyso-Gb1 assay for Gaucher's disease.

Dr Clara Van Karnebeek discussed neurometabolic disorders and her multi-omics approach to diagnosis. Stressing that while the development of diagnostic algorithms vastly improves diagnostic yield, the interplay between environment, metabolism and the genome means that a holistic approach is often required in complex disease cases.

This multi-omics approach was exemplified in the case of an 8-year-old male child that presented with microcephaly and severe epilepsy. Seizures were found to be responsive to vitamin-B6 therapy, however, routine metabolic and genetic testing for known causes of vitamin-B6 responsive epilepsy were all negative. Targeted metabolic profiling showed a low serine, high citrulline, increased lactate and ammonia and redox abnormalities including low NAD.

Whole-exome sequencing of this child revealed mutations within GOT2 – a malate-aspartate-shuttle component, a co-factor of vitamin-B6 and key regulator of NADH:NAD⁺ balance. This perturbation of NADH:NAD⁺ ratio leads to the observed lactate and ammonia accumulation and down-regulation of serine biosynthesis. Supplementation with serine appeared beneficial in this patient; furthermore, *in-vitro* GOT2 models have implied that pyruvate supplementation may also help in this disorder. Clara reflected that GOT2 mutations appear to be the fourth identified mechanism for defects within the malate-aspartate-shuttle, so called MARS defects, all of which may benefit from nutritional support.

Dr Van Karnebeek then discussed a cohort of patients with developmental delay, progressive ataxia and, in one instance, cerebellar atrophy. Initial metabolic investigations showed only an elevated glutamine, however, guided by this finding, patient derived fibroblasts were generated and shown to have an increased ratio of glutamine to glutamate and a reduction in transcribed glutaminase protein (GLS). After ultimately performing whole-exome sequencing, careful review of the data implicated GLS when a GCA-repeat expansion tract was identified in the 5' UTR of the GLS gene. Typically only 7-25 repeats are observed in a normal individual but this patient cohort showed >600 copies leading to repeat-mediated chromatin changes and down-regulation of the transcribed RNA.

Dr Julien Baruteau then presented his group's work on the use of adeno-associated virus (AAV) vectors for gene therapy to treat the urea cycle defects arginosuccinate lyase (ASL) deficiency and OTC deficiency. Murine models of the two urea cycle defects can be used in conjunction with a ureagenesis assay (Opaden et al., 2016 *Mol. Genet. Metab.*) where oral C13-acetate can be used to track hepatic disease burden. Transfection of these mice with the AAV vector gene therapies could rescue deficient hepatic ureagenesis; however in the case of ASL mice, neuronal disease persisted even in the absence of hyperammonaemia. This observation led to a second gene therapy approach whereby a liver and brain targeted AAV vector was utilized, rectifying both ureagenesis and neuronal dysfunction (Baruteau et al., 2018 *Nature Comms.*).



Pat Portnoi has had a long-distinguished career working in dietetics. She first started working with inherited metabolic disorders (IMD) in 1981 when she became a dietitian at Scientific Hospital Supplies (later to become part of Nutricia). Pat joined the company at a very exciting time. There was prolific development in 'Foods for Special Medical Purposes,' particularly for PKU, and it saw the birth of the Anamix, Maxamaid and Maxamum range of metabolic products for IMD. Pat provided an invaluable nutritional support service for IMD dietitians – she guided us through using these novel products, working together with her close colleague Pat Wallace. She soon started travelling worldwide to work with other IMD professionals and was appointed one of the first female directors of the company in 1990. In 1987, she started the DMIMD conference and although it had small beginnings – it started off as an informal meeting on maternal PKU – it soon grew into a very popular and successful international meeting. She did much to encourage dietitians to undertake research and innovation.

She was part of the steering group for the classic study on 'untreated PKU' that was conducted in adults in the UK.

In the 1990's Pat retired from SHS but started working as dietitian advisor for the Galactosaemia Support Group in 1998. She has certainly done much to improve and direct the dietary management of galactosaemia. Since 2000 she has organised the systematic analysis of the lactose and galactose content of almost 200 cheese samples, identifying several types suitable for galactosaemia. She has published extensively on cheese and galactosaemia as well as estimating the galactose content of butter and other animal fats, fruits and vegetables. She established and managed the Galactosaemia Support Group register. She has campaigned for 'warnings' on food labels about the unsuitability of foods such as 'low lactose milk' for galactosaemia. She has conducted research examining patient dietary practices, particularly in older patients with galactosaemia, as well as examining the suitability of soya infant formula for infants with galactosaemia.

She played a prominent role in the development of the dietary recommendations in the International Guidelines for Galactosaemia (Welling et al 2017). There were several international phone conferences held to debate these dietary guidelines, and some pressure was put on the UK dietetic representatives to restrict some of the galactose containing foods (without direct evidence) that we had permitted for many years. Pat elegantly negotiated a way forward using all her diplomatic skills which meant that no further foods were removed from our conventional low galactose diet. She also has produced many practical advice sheets for caregivers and patients with galactosaemia; Easter and Christmas will not be the same without her low galactose lists.

Even in retirement Pat remains an active member of the BIMDG's dietitians group TEMPLE (Tools Enabling Metabolic Parents' Learning) project which continues to produce teaching booklets/slide sets for parents of children with IMD. Hopefully Pat will now have time to spend and enjoy her many hobbies with her family. We thank Pat for a lifetime of wonderful contributions to the world of dietetics and IMD- we owe her so much!

In Memoriam / Legacy

A gift in memoriam is a powerful way to remember a loved one. **The BIMDG In Memoriam Fund** aims to benefit from the generosity of BIMDG members and their families who chose to request that friends and family make a donation to the fund in lieu of giving flowers at a funeral or memorial service. The BIMDG In Memoriam book will be used to record all such gifts providing a permanent record of each individual and all donations in their name.

Your will says what will happen to your money, property and possessions after you die. Any donation will either:

- Be taken off the value of your estate before Inheritance Tax is calculated
- Reduce your Inheritance Tax rate, if more than 10% of your estate is left to charity

Leaving a gift to the BIMDG in a will allows us to specifically support members with research, studentship and travel grants and will contribute towards the training and education of the next generation of those involved in the care of individuals with inherited metabolic disease.

Expression of Interest

Expressions of interest sought for role of BIMDG stakeholder & consultations officer

The BIMDG committee is looking to identify from within its members or elected committee an individual to take on the voluntary role of 'BIMDG stakeholder & consultations officer'. This person will be responsible for reviewing public consultation / stakeholder requests (eg from NICE), determining which the BIMDG should respond to and providing the final draft response to the committee for review. It is not expected that the officer should write each response alone but rather that he / she identifies an appropriate expert from within BIMDG to lead on each request and supports this individual to produce a response within the expected timeframe and criteria.

Ideal characteristics for this role:

- Organised, efficient at sticking to tight deadlines
- Good general understanding of a wide variety of inherited metabolic disorders
- Ability to read, assimilate and summarize scientific and medical literature succinctly
- Interest in the appraisal process of medications for inherited metabolic disease
-

Anyone interested in the role should contact elaine.murphy8@nhs.net for further information.

Outstanding Membership subscription fees

Rob Barski

It was agreed at the BIMDG 2017 AGM to increase the subscription fee from £15 to £25 for 2018. A significant number of members have still not amended their standing order accordingly for this year's membership. People who have not yet done so will need to do the following two things:

1. Pay a "top up" fee for this year's subscription of £10.
Bank details for payment:
Account Number: 04008782
Sort code: 60-16-19
Please include your name in the transfer reference so we can identify who the payment is from.
2. Amend their standing order for payment to the BIMDG to £25 for 2019 and beyond.

Failure to do so will result in not being able to take advantage of the rescued membership rate at the annual symposium as well as being unfair to the majority of BIMDG members who have already updated their subscriptions.

BIMDG Hon Treasurer