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Welcome to the latest issue of BSHG News, which has a ‘forward-thinking’ theme. The issue begins with an article from our Chair who asks “What’s in a name?” This article opens the debate regarding the name of our society and what we, as a membership, want this name to represent. We are also very fortunate to have a thought provoking article written by Andrew Read. Andrew presents his personal insight on the future of genetics in this genomics era, ideas that I’m sure will fuel many a discussion over the following weeks.

As always, we have a number of updates starting with a series of articles from the National Institute for Health Research (NIHR) Genetics Specialty Group. This is followed by progress reports from the DDD Project and the NHS National Genetics Education and Development Centre. The paediatric DNA repair disorders genetic screening service provided by The Northern Genetics Service is highlighted in this issue’s service developments section. I am also pleased to announce that the National Genetics Reference Laboratory Manchester will continue to provide updates on their initiatives despite changes to their funding.

This newsletter relies on you to identify topics that may be of interest to the membership. If you have any ideas for future articles or features, please get in touch with me. My details can be found at the end of the main section.

What’s in a name?
John Burn Chair, BSHG

Names carry great significance. They go before us, shaping the opinions of others, tethering us to a communal history, sometimes imposing an unnecessary constraint. Our working party on the structure and function of the BSHG has had two very productive meetings. There is a general enthusiasm for taking advantage of the merger of the ACC and CMGS to complete the process begun 18 years ago: to achieve the economy of scale and increase our impact on the external world by functioning more closely as a single Society comprising defined professional associations and cross cutting groups with a common purpose.

Does our present name best describe our nature, function, role and aspirations? There is a general agreement in our working party that this is the moment when our whole community should revisit the names of our groups, associations and societies to decide how we want to be labeled. A formal list of options is being prepared which includes several permutations but one word which seems to have general approval is the term “genetics” in preference to the word of the decade, “genomics”. The former was coined by Bateson in the early years of the 20th century to describe the study of hereditary traits while the latter is attributed to Victor McKusick, whose search for a name for their new journal, merging genes and chromosomes, initiated a cascade of terms, “the omics,” which have come to embrace the biological sciences.

The list of names which emerged from our latest working group discussion will be used to stimulate debate. This is not a pivotal issue but it’s one we should begin to explore. The name ‘BSHG’ has a history and is a recognised ‘brand’, but does it continue to represent our membership and role?

It is interesting that representatives of the main sections of the BSHG showed no enthusiasm for use of the term “genomics”. It was perceived to be both too broad to describe our functions and probably too transient. As molecular biological techniques become fully absorbed into, say, microbiology, it can be argued that the use of “genomics” will fade. Attention is shifting to epigenomics, transcriptomics, metabolomics, proteomics. These other “omics” are closer to phenotype and will displace linked DNA polymorphisms in research and service applications.

The converse argument is that “genetics” traps us in the past, perceived to be preoccupied with linkage analysis in families when most work in the research labs and in the regional genetics centres tends to be focused on the individual and, at most, their first degree relatives. The term is already in use by our sister organisation, the very successful Genetics Society, first launched as the Genetical Society by Bateson himself in 1920. The recently retired president of the Genetics Society, Veronica van Heyningen continues to be an active and influential member of BSHG and was quick to point out the potential for disagreement and confusion. She argues that “Human Genetics” remains the best term to embrace our collective activities and keeps us in line with our European and American “sister” societies. The Genetics Society has a session in our autumn meeting and we are running a joint meeting next spring so there will be plenty of time to debate these and related issues in the bars and eateries in the coming months.
Where’s it all going?
A personal view

Andrew Read, Genetic Medicine, St Mary’s Hospital, Manchester

I was asked to write a ‘horizon scanning’ piece. The time you usually scan the horizon is when you’re lost in the desert. You don’t know where you are or where you’re going so you desperately scan the horizon for any clue. Well, that figures. The pace of change in genetics is quite frightening, isn’t it? Frightening but also exhilarating. It’s all happening so fast, who knows what the next 20 years may bring?

The one thing that seems certain is that it’s going to be sequencing, sequencing and more sequencing. If second-generation sequencing has changed everything, just wait for third-generation, or fourth-generation. In some ways genetics is becoming much simpler. No need for clever family studies or brilliant clinical insight, just get in there, sequence the whole thing and then try to work out the meaning of all the data. Yes, you say, but there’s the rub – you end up in a morass of variants of unknown significance, and it would be madness to base a clinical service on uninterpretable data.

Well, I’m not so sure (about the uninterpretability, not the madness). Look how Google has changed our lives. Consider a non-genetic example. I like old books. I buy them for their content, not their covers. I have a splendid 18th century cookbook full of wonderful recipes, like how to dress a 100-pound turtle. It’s in very bad condition, minus its covers and title page, which is why I could get it for a pound or two. I thought it would be worth getting it rebound to preserve it and nice to find an image of the title page to bind in. It took me about two minutes on Google to find the image I wanted. Ten years ago that would have been unthinkable. And in genetics? Already we have the Seattle database and we’re moving from the 1,000 Genomes Project to the 10,000 Genomes Project – what will we have in ten or twenty years?

With vast databases and efficient search engines, the current requirement for heavy bioinformatics expertise may be a passing phase. Of course, there will always be variants of unknown significance, but I think that in ten years, or at most twenty, there will be very few unknowns that are of major clinical significance. With data on a million genomes, it will be much clearer which parts of which coding or non-coding sequences can host variants with major pathogenic effects. I think that whole genome sequences will be as cheap and at least as reliable as many other standard diagnostic tools – as long as we are talking about variants with major effects.

It’s the variants with minor effects that are intractable - things that have insignificant effects on their own, but might become significant as part of a combination of variants. ‘Predict and Prevent” failed because it was scientifically flawed. You need special circumstances for a variant to be both common and significantly deleterious. Adding together the risks of individual disease-associated SNPs just hasn’t, in most cases, given predictions strong enough to be useful. There will be exceptions – there already are in age-related macular degeneration, for example. Added to which, predicting without the ability to prevent is of limited value, and GWAS has not provided the hoped-for goldmine of high-grade targets for preventive drug treatments.

Will that change as studies get ever larger, and as we gradually move from linked SNPs to the true causal variants? I rather doubt it. No doubt there will be some successes, but I think the real problem is the sheer complexity of much complex disease. Cecile Janssens has a rather nice analogy between complex disease and major accidents. The Herald of Free Enterprise didn’t capsize just because the
“One thing I do see looming large is non-invasive prenatal diagnosis”

One thing I do see looming large is non-invasive prenatal diagnosis (NIPD). I could easily imagine NIPD being the next ‘big thing’. Dennis Lo showed that it is technically possible to deduce the complete fetal genome from analysis of both parents and free DNA in maternal blood (although he had to sequence the maternal blood DNA to 65x depth, and the cost was astronomical). Maybe there will be scientific reasons why his procedure will never be reliable. However, if the limitations are purely technical then in a few years it is likely those limitations will be overcome and I can imagine there being a large demand for genomewide NIPD. Again, it will only predict mendelian and near-mendelian phenotypes not complex disease. But if, as the 1,000 Genomes data suggest, we each carry around 100 non-functional gene variants (not counting CNVs and reduced-function variants), the clinical and health-economic case for universal NIPD could be strong. Internet companies might offer all manner of dubious services for parents who fancy breeding Olympic athletes or musical prodigies – but there should still be a substantial core of clinical utility for this test to be considered as part of routine NHS service once costs have fallen far enough.

What about personalised medicine? As far as this means pharmacogenetics, I’ve been a bit of a sceptic. All those cytochrome P450 variants have been known for years, but they didn’t alter clinical practice. Clinically useful knowledge about P450 effects has come from knowing which drugs induce or inhibit gene expression, regardless of genotype, to identify potentially dangerous drug interactions. Maybe things are changing. The effect sizes for pharmacogenetic variants are large compared to the effect sizes of complex disease risk factors, so the potential is there for genotyping to be useful. Cases where genotyping is mandatory or advisory before prescribing are also accumulating. However, we have to think about the economics. It’s not in the financial interest of drug companies to develop tests that limit the market for their drug to only those patients where it might actually work – unless the drug is so expensive that NICE would insist on that. It would, however, be in their interest to develop tests to exclude patients who might suffer severe adverse effects, and there are now some examples of this. One thing that will move this forward is development of real-time bedside genotyping technology.

Certainly personalised medicine has arrived in a big way in cancer treatment with stratified cancer treatment one of the big success stories of the last few years. Imagine the impact on treatment of other common diseases, such as psychoses, if we were able to categorise these common conditions into genetically more homogeneous subgroups. However, for many common diseases, even those that are genetically heterogeneous in their pathogenesis, the major drug targets are in well-understood final common pathways. So I’m hedging my bets on personalised medicine.

The Joker in the pack is epigenetics. We don’t know how far epigenetic marks are heritable from parent to child, and thus how far they might explain the ‘missing heritability’ of complex diseases. We do know, however, that they control chromatin flavours and hence the relation of DNA sequence to cellular phenotype. Up to now, clinical service studies of epigenetic effects have always been targeted and limited to a dozen or so conditions. Will we see genomewide epigenotyping in routine service? Histone modifications can now be catalogued on a genomewide basis, but this has been a specialised area, not ripe for clinical application. Some of the newer sequencing technologies can reportedly identify methylated cytosines, so at least one aspect of the epigenome may become accessible to routine genomewide analysis. But there is a problem – or maybe it’s an opportunity, because genome analysis...
could potentially be a wonderful job creation scheme for geneticists. We each have only one genome (well, OK, one from each parent), but we have dozens, maybe hundreds of epigenomes, each specific to a particular tissue and maybe also a particular time in our life. So how far will these undoubtedly important effects be accessed in clinical service? A routine blood or mouthwash sample can show us only one epigenome. My guess is that an epigenetic scan will be part of the pathology work-up of many biopsy specimens, but I have difficulty imagining any sort of general epigenetic work-up of a whole patient.

The common theme in this bleary-eyed horizon scanning is a convergence of all clinical genetic laboratory procedures. Now we use specific techniques to identify genetic alterations (such as karyotyping, FISH, CGH, MLPA, Sanger sequencing etc.). However, we may end up with single-molecule sequencing of unamplified DNA or cDNA with the results effortlessly checked against vast databases. This may not be a very enticing vision. It could so easily all get centralised in a few huge labs run by rapacious companies and staffed by de-skilled technicians. Keeping the tight linkage between the laboratory and the doctors is one important line of defence, and the stratified medicine approach may suggest a model. Another would be to come up with technologies to prevent the convergence. Something defensibly genetic that can make important predictions of disease that cannot be made by sequencing DNA – something proteomic, maybe, reflecting the epigenomes of inaccessible tissues. Fortunately the one thing we know for sure about the future is that it never turns out how we predicted.

1. NIHR Genetics Clinical Research Studies: How can we help?

Studies which may have previously struggled to get off the ground, or been cancelled part-way through, are now meeting with success thanks to support from the National Institute for Health Research (NIHR) Genetics Specialty Group.

Regulatory barriers can often impede new clinical trials, with long waits for research and development approval delaying the recruitment process. But now there’s help at hand.

"We can reduce red tape, or help cut through it quickly," explained Group Chair Sir John Burn, Professor of Clinical Genetics at Newcastle University.

"The Specialty Group also gives better access to wider patient populations and a network of skilled research support staff," he added. Such staff will work to consent and recruit patients into relevant trials and perform any necessary procedures.

The Deciphering Developmental Disorders (DDD) project, which aims to study the genomic basis of severe developmental disorders to improve their diagnosis and management, has benefited greatly from this support. Thanks to help from the NIHR Collaborative Group for Genetics in Healthcare (CGGH), working with the NIHR Genetics Specialty Group, DDD received research and development approval to recruit from all 23 regional genetic centres only eight months after the initial grant was awarded and had recruited 750 people within 6 months.

"There is a uniformly high quality in NHS genetic services, and the Specialty Group offers great opportunities for collaborative research," said Dr Helen Firth, a consultant clinical geneticist at Cambridge University Hospitals Trust, who co-manages the project.

The Genetics Specialty Group is one of 24 topic-specific groups within the NIHR Comprehensive Clinical Research Network (CCRN); part of the NIHR Clinical Research Network which provides researchers with the practical support they need to make clinical studies happen in the NHS. The CCRN is made up of 25 Comprehensive Local Research Networks (CLLRNs) which facilitate these services at a regional level.

"The added support of CLRNs has allowed us to meet our targets and extend the range of demographic areas we have included," commented Professor Lyn Chitty, lead researcher on the RAPID (Reliable, Accurate Prenatal non-Invasive Diagnosis) project. This is a five-year project funded by an NIHR Programme Grant, to develop better techniques and clinical standards to inform the implementation of non-invasive prenatal diagnosis (NIPD) when appropriate.

To benefit from this support a study must first meet specific eligibility criteria (http://www.crncc.nihr.ac.uk/about_us/processes/portfolio/p_eligibility/) set by the Department of Health. Those studies then become part of a national database of research known as the NIHR Clinical Research Network Portfolio (http://public.ukcrn.org.uk). The database also captures study recruitment data which is used to performance manage trials to time and target and to assess feasibility of new studies. Importantly, data from the Portfolio is also used to allocate NIHR research resources.
“What we’re hoping to achieve is a ‘one signature fits all’ approach”

While the group was funded to support clinical trials, it has also been used by social scientists studying the social and ethical aspects of genetics. Dr Janice McLaughlin said her Economic Social Research Council funded three-year ethnographic study of children and families being seen by paediatric genetics clinics gained “kudos” as an NIHR Clinical Research Network Portfolio study. The Network supported the fieldwork aspects of the study and opened up opportunities for useful dissemination.

These comments were made at an education session about the collection of studies supported by the NIHR Genetics Specialty Group during the British Human Genetics Conference in September 2011.

2. Working together in 2012: Cutting through red tape for clinical geneticists

Genetics professionals should have better ways of working together by the end of 2012, according to Professor Sir John Burn, Chair of the National Institute for Health Research (NIHR) Genetics Specialty Group.

As one of 24 topic-specific groups within the Comprehensive Clinical Research Network (CCRNI), the NIHR Genetics Specialty Group aims to improve efficiency in clinical studies by providing researchers with access to support staff and wider patient populations.

But a major target is to squeeze out the associated bureaucracy, with Professor Burn saying that it was imperative that the process doesn’t strangle the outcomes.

Referring to the barriers of the human tissue act, anxiety about breaches of confidentiality in genetics and genomics, and numerous Foundation Trust governance issues, he said the group wanted to make it easier for people in genetics to work together.

“What we’re hoping to achieve is a ‘one signature fits all’ approach - so if a non-interventional, low-cost project is approved by a Foundation Trust that is home to a regional genetics centre, then that approval should be good enough for everybody else,” he explained.

This is particularly important in studies involving rare diseases, as in some regions there are very often more administrators involved than there are patients with the disease.

The idea has met with the approval of both the researchers and the Foundation Trusts themselves, who spend large amounts of money on such governance evaluations. This is a cost Professor Burn labels “disproportionate”, particularly if the region in question has only one patient, and believes it “effectively kills the research”.

To facilitate this process, the NIHR Collaborative Group for Genetics in Healthcare (CGGH), is developing a suitable agreement with the support of the NIHR Office for Clinical Research Infrastructure (NOCRI).

Professor Burn hopes that the development of a formal agreement will be the big breakthrough of 2012 and result in increased numbers of recruitments to genetics research studies. He also hopes that it may pave the way for a reduction in red tape in clinical research as a whole.

A longer-term plan of the NIHR CGGH is to look at the informatics systems used by clinical geneticists, something which was also touched on in the report released by the Human Genomics Strategy Group at the start of the year.

“Genetics services have grown up organically, with all manner of different systems and intellectual property support structures,” Professor Burn said. “We need to be thinking about how we progress to a shared database.”

The NIHR CGGH hopes to drive the idea of a shared database forward over the next two years.

3. Imprinting research takes a national approach and challenges widely held beliefs

Overlaps in imprinting disorders could lead to misdiagnosis or incorrect treatment, according to ongoing research at the University of Southampton.

Genomic imprinting causes one of the two copies (alleles) of a gene to be silenced, dependent on which parent the allele came from. Silencing occurs through a process known as epigenetics – modifications, such as the addition of chemical groups, to the genome that do not affect the DNA sequence itself. It results in certain genes being expressed from one allele only, and may happen in specific cells. Imprinted genes are crucial for normal human growth.

Errors in this process result in imprinting disorders, such as Prader-Willi syndrome, and are often associated with developmental problems as well as disordered growth. Due to a wealth of similar and rather non-specific symptoms
“We were keen on having medical groups involved in the project...we couldn’t have done the work without that kind of collaboration”

like failure to thrive, there are often problems with diagnosis, which can lead to difficulties when treating a patient and giving advice on long term prognosis. The research, being carried out by the Wessex Imprinting Group (http://www.southampton.ac.uk/geneticimprinting) at the University of Southampton aims to assess how widely these changes in imprinting are (UK Clinical Research Network study 4917 IDFOW Imprinting Disorders, http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=4917).

Project clinical lead Professor Karen Temple explains: "We think that some people with one imprinting disorder may have errors at many other imprinting loci. At just one locus, you might assume there is an underlying genetic rearrangement to account for the epigenetic changes, but if there’s more than one, we have to wonder if it’s a global factor. This research aims to find out what they are."

Without knowing about imprinting errors elsewhere in the genome the standard treatments may not be adequate. For example patients might be susceptible to other associated risks; some epigenetic changes have an increased chance of developing cancer and without testing this might not be realised.

Professor Temple hopes that eventually a genetic test will be developed for imprinting disorders that will test all the potential loci in one go. This would also improve treatment on an individual basis, she explains, as currently everyone with one diagnosis is given the same treatment but comprehensive epigenetic testing could stratify disease and improve medical management.

"If we can learn more we’ll increase our chances of knowing which expensive treatments are worthwhile," she says. "Making far more in depth diagnoses will lead to better and more personalised medicines."

The research involved recruiting large numbers of patients with rare diseases from across the UK; something which Professor Temple explains couldn’t be done without the help of the National Institute for Health Research Comprehensive Clinical Research Network (NIHR CCRN).

"We used to be able to do studies in our spare time," Professor Temple says of herself and other clinical geneticists. "But now it is done much more professionally – CLRNs employ a nurse specifically for this in each genetic centre, and it makes a huge difference."

Another important outcome Professor Temple highlights is that "very rare patients give us insights into common disease mechanisms" – knowledge gained about the factors involved in genetic imprinting could offer clues about normal human development, as well as long term non communicable diseases such as diabetes.

4. How collaboration between social scientists and the NIHR Genetics Speciality Group facilitates good practice in research

Researchers investigating the social and personal implications of genetic investigations of children have benefitted from collaborations with the National Institute for Health Research (NIHR) Genetics Specialty Group. The three-year Economic and Social Research Council (ESRC)-funded ethnographic study, led by Dr Janice McLaughlin, a sociological researcher from the Policy, Ethics and Life Sciences (PEALS) Research Centre, recruited and followed 26 families from paediatric genetics clinics in the north of England.

Dr McLaughlin wanted to build strong, long-term relationships with the clinics from the start. “We were keen on having medical groups involved in the project, not just linked to it, so geneticists are part of our team”, she explained. "We couldn’t have done the work without that kind of collaboration”.

This was where the NIHR Genetics Specialty Group came in. They provided Dr McLaughlin’s team with specific support, not only during the process of gaining research and development and ethical approval, but also improving the recruitment process.

“It’s made a huge difference, having the kind of access to clinicians we had. They identified families that matched our criteria, helping our research design and ensuring we worked within the appropriate ethical boundaries in relation to handling patient personal data”.

Anonymity and sensitivity are major issues in such studies, and the clinicians’ extra knowledge is invaluable – ensuring recruitment letters were not sent to families whose child had died for instance. “We quite rightly do not have access to medical records to look for possible participants. That the clinics handled this side of things helped a great deal. By working together we achieved something more” Dr McLaughlin explained. She was quick to point out that, while practitioners supported recruitment, the clinics were independent
“A geneticist may be interested in identifying the specific chromosomal anomaly, while families are focused on the effects on the child’s life.”

Over time, however, parents often began to be less focused on finding ‘the answer’, recognising that it is hard to know what lies ahead for any child”. Dr McLaughlin continued “They became more at ease with the uncertainties of what genetics can tell us”.

Additionally, the idea they may have unknowingly passed something on to their child troubled some, and even if they found out that wasn’t the case “there was other family and community dynamics around blame and responsibility”.

For many, though, a diagnosis was valued for the help it provides in terms of access to support, an explanation for why their child is different and also providing some avenues for treatment.

“It may be surprising,” Dr McLaughlin commented, “but some parents and children took pride in their genetic uniqueness.”
Preparing nurses and midwives to deliver genetic-genomic healthcare

Emma Tonkin and Maggie Kirk, Genomics Policy Unit, University of Glamorgan
Heather Skirton, Plymouth University

It is well accepted that guidelines setting out minimum standards of competence in genetics are necessary to support health professionals develop their practice appropriately. In the UK, such competences for the nursing professions have been available since 20031. Recognising the pace of genetics/genomics research, the team that undertook this original work recommended that a review of the framework take place within 5-10 years. In the intervening period, our knowledge and understanding of genetics and genomics has grown significantly and its translation into patient benefit continues. As such, nurse education and training must reflect this changing face of healthcare. To review this framework, two national meetings were held involving practitioners, educators, patient representatives and policy makers, where real stories from patients, family members and professionals were used to focus discussion. Items generated during each meeting were mapped to the current ‘joint’ genetics framework for nurses and midwives, and gaps and content that required updating were identified and changes made. Two frameworks tailored for each profession have now been produced; each setting out the minimum competence that should be required at registration. These frameworks provide a foundation of core competence that can be built upon as an individual becomes more experienced and/or a role changes to incorporate new knowledge or technological advances. The importance of genomics within healthcare is now explicit and anticipating that the implementation of new knowledge and technology will impact both nursing and midwifery, the team have endeavoured to “future-proof” the frameworks.

Fit for Practice in the Genetics/Genomics Era – Nursing

Revisions were made to all of the original seven statements and following consultation the revised framework was approved. The overarching statements of the framework are set out in Box 1. Additional detail accompanies each statement and is available at: http://www.geneticseducation.nhs.uk/media/45814/fpgge%20learning%20outcomes%20for%20nurses%20report.pdf.

Box 1. The overarching statements of the revised nursing framework

1. Identify clients who might benefit from genetic services and/or information through a comprehensive nursing assessment
2. Demonstrate the importance of sensitivity in tailoring genetic information and services to clients’ culture, knowledge, language ability and developmental stage
3. Advocate for the rights of all clients to informed decision making and voluntary action
4. Demonstrate a knowledge and understanding of the role of genetic/genomic and other factors in maintaining health and in the manifestation, modification and prevention of disease expression, to underpin effective practice
5. Apply knowledge and understanding of the utility and limitations of genetic testing and information to underpin care and support for individuals and families prior to, during and following decision-making
6. Examine one’s own competency of practice on a regular basis
7. Obtain and communicate credible, current information about genetics, for self, clients and colleagues
8. Provide ongoing nursing care and support to patients, carers and families with genetic healthcare needs

Statement 1 now reflects the need to include family history information as part of a comprehensive nursing assessment, which is implicit in the new Nursing and Midwifery Council guidelines. Statement 6 emphasises the responsibility of nurses to keep up to date in their own area of practice. Importantly, a new competence (Statement 8) has been added that highlights the importance of ongoing nursing care to address the needs of both the individual and their family/carer that may change over time.

Detailed learning outcomes for all eight statements are aligned to the stages of UK pre-registration training, and practice indicators provide a tool to facilitate knowledge and skill development for those already qualified and their managers. The full
Mind your p’s and q’s

Peter Harper, Institute of Medical Genetics, Cardiff

A few years ago, while making recorded interviews with a number of the founders of human cytogenetics, I realised that the question of nomenclature in this area had generated as least as much debate and controversy as in most others. The 1960 Denver report and the subsequent ISCN committee reports succeeded in establishing and maintaining a remarkable degree of unanimity, but the origin of some of the terms used remains unclear. In particular, why the letters p and q were chosen to denote the short and long arm of a chromosome is debatable.

The p and q terms do not appear in the original Denver report, but were in use soon afterwards. There is general agreement, including from those present at the Denver meeting, that p was chosen to represent ‘petit’ as a concession to Jerome Lejeune, whose own Paris nomenclature had reluctantly been given up. However the origin of q is much less clear. David Harnden (present at the Denver meeting) has stated in an interview (www.gennedhist.org/interviews) that q resulted from a misprint for g (grand as opposed to petit). While in Sweden Jan Lindsten, in response to an enquiry from Felix Mitelman, is of the opinion that q was chosen as the next letter after p, after ‘grand’ was rejected on the grounds of two French terms being excessive.

A third possibility, suggested to me by the late John Edwards, is that since p + q = 1, for any chromosome q must necessarily mean the long arm once p has been designated for the short arm.

None of these suggestions is entirely satisfactory and no definitive source has so far been identified to clarify the origin of p and q. If any cytogeneticist or historian can help to clarify matters, please let me know (HarperPS@cf.ac.uk).

Incidentally, a comparable uncertainty seems to surround the aphorism which I have used as a heading for this note. To ‘mind your p’s and q’s’, meaning to be on your best behaviour, seems to have been in the English language for two or three centuries, but consulting the Web shows a number of possible origins. One suggestion is that it was an exhortation to young children not to reverse their letters by confusing p with q; alternatively the message might have been for print compositors when placing type in a frame.

There is even a French possibility of watching one’s feet (pieds, p) and one’s wig (queue, q), apparently given by French dancing instructors to their pupils. Jerome Lejeune would surely have approved of this!

BMA Medical Book Award – Dr Dorian Pritchard

The BSHG is delighted to congratulate Dr Dorian Pritchard (former Lecturer in Human Genetics at the University of Newcastle) who, along with co-author Professor Bruce Korf (Chairman of the Dept of Genetics, University of Alabama) and publishers Wiley-Blackwell, was awarded a first prize in the Medicine category of the BMA Medical Book Awards, for their book, “Medical Genetics At A Glance” (2nd Edition ISBN: 978-1-4051-4846). A reviewer commented “This book provides an extremely extensive introduction to the complexities of modern molecular and clinical genetics for students and anyone coming to the field for the first time.”

The award should have been presented by Professor Richard Dawkins in 2008, but due to the confusion surrounding the merger of John Wiley Ltd with Blackwell Publishing, the authors were not notified. This oversight was only recently discovered when one of the authors Googled his own name! The 3rd Edition of this book will be available early 2013.
DDD Project Progress Report

Caroline Wright, DDD Project Manager on behalf of the DDD project, Welcome Trust Sanger Institute, Cambridge

The Deciphering Developmental Disorders (DDD) project, which is a collaboration between the Wellcome Trust Sanger Institute and all 23 NHS Regional Genetics Services, is now well into its second year of recruitment. At the date of writing, over 120 clinical geneticists had recruited a patient to the DDD study and collectively we have recruited around 2,000 children with severe undiagnosed developmental disorders and their parents, from all around the UK. Families are consented by their local clinical team, who also enters detailed patient information and phenotypes online using a dedicated DDD-study entry portal via the DECIPHER database.

We undertake genomic analysis on the blood-DNA samples from the child, sent to us by regional genetic laboratories, and on the saliva samples sent to us by the families. We have now completed high resolution microarrays analysis on over 1,000 patients and exome sequencing of over 200 trios (the affected child and both parents) with hundreds more in the pipeline.

Scientists at the Sanger Institute are now focused on developing scalable and robust analyses so that we can feedback variants to local clinical teams with high specificity (ensuring we do not report variants with a low likelihood of being causal) and high sensitivity (ensuring we do report variants with a high likelihood of being causal). Following stringent quality control of the data, this involves a number of filtering steps:

- Removing common variants by comparison with our control datasets
- Removing variants where the inheritance is inconsistent with family history
- Removing any variants where data from different assays disagrees
- Removing small variants (deletions <100kb, duplications <250kb) unless they overlap a gene already known to be associated with developmental disorders

Variants that overlap known development disorder genes are further filtered based on:

- allelic status versus genotype
- mutation consequence versus variant type
- published phenotype versus patient phenotype

Feedback of potential causal variants to regional genetics services will be rolled out in two phases via DECIPHER. The first phase will focus on copy number variants identified using arrays, which could include anything from a single exon deletion to a multi-megabase duplication. In the second phase, we aim to roll out a similar system, with extended filtering, for single nucleotide variants and small insertions/deletions identified using exome sequencing. Our trio-exome sequencing strategy has allowed us to rapidly identify potentially causal de novo single nucleotide variants in a number of children, as well as investigate other genetic models. We are in the process of developing high-throughput validation assays for these sequencing variants using next generation sequencing technology (as well as Sanger sequencing in the first instance) before reporting any variants back to clinical teams. We are also investigating their potential function impact in silico using numerous databases and pathogenicity scores, and in vivo using zebrafish as model organisms.

In addition to the scientific research and translational aims of project, we are investigating the ethical implications of genome sequencing and public opinion toward data sharing and dealing with incidental findings. We recently launched an online survey, using bespoke short videos to explain some of the complex concepts involved in this area and are encouraging everyone interested to complete the survey online (www.genomethics.org).

After a successful DDD meeting in February – at which research nurses and genetic counsellors who are driving recruitment in each of the regional centres visited the Sanger Institute – we held another larger meeting at the end of May for clinicians and laboratory scientists to update local teams on progress and discuss the clinical feedback pipeline. This was the first meeting where Matt Hurles officially took over as lead Principal Investigator, after Nigel Carter’s retirement at the end of April. We are all very grateful to Nigel’s leadership and continued involvement in both the DDD and DECIPHER projects, and wish him a happy retirement in sunny Cornwall!

Acknowledgements

The DDD study is co-funded by the Wellcome Trust and Department of Health, through an award from the Health Innovation Challenge Fund [grant number HICF-1009-003] and the Wellcome Trust Sanger Institute [grant number WT098051]. The research team acknowledges the support of the National Institute for Health Research, through the Comprehensive Clinical Research Network.
Update from NGRL Manchester

Department of Health funding for the NGRLs ceased at the end of the 2011/2012 financial year. So what does this mean for NGRL Manchester?

Sustainability for our services was always a planned part of the funding agreement, and during the last 18 months our efforts have been focused on achieving this. In essence, it is more or less business as usual – NGRL Manchester will continue to provide services, research and consultancy in bioinformatics and health informatics to support the UK genetic testing network. Our scope has broadened to encompass an international community, bringing the benefits of global data sharing and research efforts to the UK laboratories. Moving forward, NGRL Manchester’s work programme will comprise four core services (DMuDB, SNPCheck, bioinformatic resource analysis and bioinformatic training), supported by related grant funding and consultancy.

DMuDB
DMuDB is widely recognised as an important repository of unique clinically validated data. Recent analysis demonstrated that approximately 68% of the variants recorded in DMuDB are not available in other readily accessible databases. This statistic highlights the importance of DMuDB as a clinical resource, and also as a source of unique data that should be more widely available. NGRL Manchester has been exploring this for a number of years now – clearly, there are legal, ethical and regulatory issues that must be addressed. A key development is the proposal currently under consideration that DMuDB should form the UK node of the Human Variome Project (HVP). Discussion of this project and more broadly around the bioinformatics community is essential, and we will ensure that planned meetings are well publicised.

DMuDB now has more than 54 subscribing laboratories, from over 21 different countries. A steady flow of international data is being submitted. To keep up to date with new data, users can subscribe to DMuDB data alerts (email support@dmudb.net with ‘subscribe DMuDB data alert’ in subject line), or visit www.ngrl.org.uk/Manchester/page/dmudb-statistics to see a summary of data in DMuDB.

SNPCheck
SNPCheck 3 was launched in April 2012 and has replaced SNPCheck v2.1. New features have been introduced, including personalised laboratory accounts, primer storage facilities, and the ability to save results. Full access to SNPCheck 3 is available via an annual subscription on a per lab basis. Subscription provides access to the new features and enables batch checking of up to 500 primer pairs at once. Free access is still available to a limited version of the tool, which will allow the checking of one primer pair at a time. We are also working to integrate 1000 Genomes Project data into SNPCheck independently of dbSNP in order to provide users with easy access to the most recent dataset. Users can sign up to the SNPCheck mailing list (www.ngrl.org.uk/Manchester/page/mailing-lists) to receive progress updates.

Bioinformatic tool analysis
Work in this area has focused on the review and analysis of bioinformatic tools for the prediction of missense variant pathogenicity. An overview of tools is now available on the NGRL website and an analysis of their performance has been carried out. This was presented at the Joint ACC/CMGS Spring Meeting, Birmingham, May 2012. A report will be produced in due course and will be available for download from the NGRL website.

NGRL bioinformaticians have also been looking at the 1000 Genomes Project data. We have formatted the data to make key information, such as Minor Allele Frequency (MAF) scores by population group, more readily available. We are making this information available through SNPCheck 3 and are also collaborating with the professional societies to develop additional guidance and resources to help clinical scientists use this powerful dataset effectively and safely.

Grant funded projects and consultancy
Clinical Coding, This EU EEC/RDTF funded project has now been completed. The key output was an improved ontology of rare disease terms now available at Orphanet, which is being integrated into the WHO ICD11 and linked to key medical terminologies such as SNOMED-CT. NGRL is now looking into how this work can be applied to other ontology/terminology work in the UK such as the National Laboratory Medicine Catalogue.

GEN2PHEN, We are now in the final year of this project. Work is focused on two main themes – federation and sharing of variant data, and the collection of phenotype data. Workshops and meetings will be taking place during the year to discuss these matters. Input from the UK clinical genetics community is essential, and we will ensure that planned meetings are well publicised.

Consultancy, NGRL Manchester has been providing expertise in bio- and health informatics on a consultancy basis. Projects include facilitating requirements-gathering for a TSB-funded next generation sequencing informatics software project, and systems specification and gap analysis for the EMBN website and IT system.

Andrew Devereau
andrew.devereau@cmft.nhs.uk
Defects in DNA repair pathways are a well known cause of familial cancer syndromes and can also lead to rare and potentially life-limiting childhood disorders. Among these are the nucleotide excision repair disorders (xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy), the helicase disorders (Bloom syndrome, Werner syndrome and Rothmund-Thomson syndrome), Fanconi anaemia and dyskeratosis congenita. With considerable phenotypic overlap, differentiating between these disorders clinically is often difficult and in many cases genetic diagnosis has not been routinely available. Consequently, in many cases the molecular cause of the condition remains unknown.

Over the last year, the Northern Genetics Service (NGS) has developed a liquid capture and next generation sequencing screen which simultaneously interrogates the majority of known causative genes for the paediatric DNA repair disorders, alongside genes involved in the same pathways that have not yet been identified as pathogenic. Where mutations are not found in the known disease-associated genes, we hope that our approach will lead to the identification of novel causes of these conditions. This screen is less invasive than existing assays, as a skin biopsy is not required and provides a molecular rather than cellular diagnosis allowing clinicians to provide accurate genetic advice to affected families.

For patients with a suspected DNA repair disorder we can offer mutation searching in 183 DNA/transcription genes at a cost of £1600 per patient fixed until July 2013. We require at least 1ug of DNA to undertake this genetic screen, although we would prefer to receive an EDTA blood sample. A summary of the clinical phenotype will also be requested to help focus our molecular analysis and the reporting of identified variants. Putative pathogenic mutations will be reported and a table of percentage coverage >15 reads for each gene can be provided on request. We will confirm any variants found using Sanger sequencing. For a full list of genes, please contact Ruth Sutton.

**Spotlight: xeroderma pigmentosum**

Xeroderma pigmentosum (XP) is an autosomal recessive disorder characterised by extreme sensitivity to UV radiation and an increased incidence of skin cancers. Some patients also develop progressive neurological problems. Most forms of XP are caused by mutations in the genes that encode proteins involved in the nucleotide excision repair (NER) pathway, which is responsible for repairing UV radiation-induced photoproducts and other bulky DNA adducts. NER function is normal in variant XP (XPV), but defective DNA synthesis past unrepaired UV damage occurs due to mutations in POLH, which encodes a DNA damage-bypass DNA polymerase. We have had particular success with our liquid capture assay for the XP genes (see Table 1) and as a result are now able to offer cost-effective and efficient mutation searching in all of these – an important development in XP diagnosis. We are currently undertaking a similar audit of mutation coverage for Fanconi anaemia and other DNA repair disorders. This information will be made available in due course.

Table 1: Audit of liquid capture results for the XP genes.

<table>
<thead>
<tr>
<th>Complementation group</th>
<th>Gene</th>
<th>Average % Coverage &gt;15 reads</th>
<th>% HGMD mutations that would have been detected using this assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>XPA</td>
<td>XPA</td>
<td>67</td>
<td>79</td>
</tr>
<tr>
<td>XPB</td>
<td>ERCC3</td>
<td>98.9</td>
<td>100</td>
</tr>
<tr>
<td>XPC</td>
<td>XPC</td>
<td>95.7</td>
<td>100</td>
</tr>
<tr>
<td>XPD</td>
<td>ERCC2</td>
<td>80.3</td>
<td>80</td>
</tr>
<tr>
<td>XPE</td>
<td>DDB1/2</td>
<td>98.0/99.7</td>
<td>100</td>
</tr>
<tr>
<td>XPF</td>
<td>ERCC4</td>
<td>91.8</td>
<td>100</td>
</tr>
<tr>
<td>XPG</td>
<td>ERCC5</td>
<td>91.4</td>
<td>100</td>
</tr>
<tr>
<td>XPV</td>
<td>POLH</td>
<td>99.5</td>
<td>100</td>
</tr>
</tbody>
</table>
Genetics and genomics education: resources to support healthcare professionals

Silvana Ioannou, Communication Specialist
Rob Newton, Education Development Specialist

Supporting genetics education
Over the past seven years, the NHS National Genetics Education and Development Centre has worked with diverse groups of NHS health professionals to identify and meet their educational needs in genetics. We have done this through the development of high quality teaching and learning resources, courses and online education.

Following the publication of the Human Genomics Strategy Group report Building on our inheritance1 we are now focusing on the educational issues this group has identified. These include raising health professionals’ awareness of genomic healthcare and supporting university educators to incorporate relevant genetic and genomic education into their teaching programmes.

To help us better meet the needs of these groups, we will be launching a new www.geneticseducation.nhs.uk website later this year. Underpinned by sound educational principles, the new format will make our content easier to find, use and share.

Features of our new website
• A fresh new look with improved navigation including clearer labelling and search functions so that appropriate educational resources can be accessed quickly
• Links to genetics in the news providing a summary of the genetics stories hitting the headlines
• An expanded ‘I’m learning genetics’ section with structured text, animations, videos and eLearning objects relating core genetic concepts to their clinical applications

• Additional resources to support those teaching genetics such as lesson plans and structured presentations to complement the PowerPoint slide packages and clinical scenarios that are currently available
• More detailed information about genetic conditions with more extensive condition summaries including factsheets, video clips and links to relevant learning resources
• Links to our virtual learning environment ‘My genetics learning’ for access to tailored genetics eLearning programmes for cardiology and neurology trainees

One of our key aims is to support non-genetics specialists in identifying how genetics applies to them and to incorporate appropriate genetics activities into their clinical roles. Our website’s new ‘I’m in clinical practice’ section helps health professionals break these activities down into clearly defined steps and provides systematic guidance, tools and sources of further information.

Give us your views
As with all of our work, we welcome and appreciate ongoing feedback from our colleagues in the genetics community. Come and give us your views at our stand during the BSHG conference, or email us enquiries@geneticseducation.nhs.uk. We are also running an education workshop at the conference, so come along to find out more.

References

Additional service: Cockayne syndrome
For patients with a clinical diagnosis of Cockayne syndrome, we currently offer Sanger sequencing of ERCC6 and ERCC8 combined for £250 (fixed until July 2013). Turnaround times for a full gene screen is 40 days (we will expedite urgent samples), carrier testing is 10 days and urgent prenatal diagnosis for known familial mutations within three days.

Please note that cellular diagnosis for XP and Cockayne syndrome remains available through Professor Alan Lehmann, University of Sussex. A NCG-funded clinical service for XP is located at Guy’s and St. Thomas’ NHS Foundation Trust.

Contacts:
Molecular Testing
Ruth Sutton Tel: 0191 2418775 Ruth.sutton@nuth.nhs.uk

Clinical/Research Liaison
Dr Brian Wilson Tel: 0191 2418744 brian.wilson@nuth.nhs.uk

Consultant Clinical Geneticist
Dr Miranda Spitt

Head of Laboratory
Dr David Bourn
Call for participants:
tuberous sclerosis clinical trial

The TRON study (A randomised, double blind, placebo-controlled study of RAD001 (Everolimus) in the treatment of neurocognitive problems in tuberous sclerosis) is due to start recruiting. We are applying for adoption of the study by the NIHR Clinical Genetics Clinical Research Network Portfolio.

We wish to recruit 48 individuals aged 16 to 60 years with tuberous sclerosis who are seizure free or have stable epilepsy (no change of AEDs in last 6 months), and who are able to participate in direct neuropsychological tests. Eligible participants are required to have an IQ of 60 or more and we will measure IQ at screening. Eligible individuals may have normal (or even supra-normal) IQ as specific neurocognitive deficits are frequent in this group.

This is a single site study based at Cardiff University. Travel expenses, including overnight accommodation for UK patients and a family member, friend or carer where required, are funded for the study visits.

For further information on the study or to discuss potential eligibility please contact:

Professor Julian Sampson  
Clinical Professor of Medical Genetics

Dr Anurag Saxena  
Clinical Research Fellow  
Institute of Medical Genetics, Cardiff University.

Email: tron@cardiff.ac.uk  
Tel: +44 029 20746412  
Fax: +44 029 20746651

Benefits of membership of the Royal Society of Medicine

The Royal Society of Medicine (RSM) in London was founded over 200 years ago and today continues to be one of the largest providers of continuing medical education with over 400 CPD educational events every year for doctors and allied healthcare professionals. The RSM promotes the exchange of information and ideas on the science, practice and organisation of medicine. The Medical Genetics section fosters collaborative thinking to forward knowledge and the understanding of genetics in medicine and society, and organises events such as the recent meeting entitled Essentials of medical genetics for clinical practice today.

Membership of the RSM not only guarantees reduced rates on educational meetings, but access to other benefits such as the RSM library. The library features a state-of-the-art internet search platform for journal access as well as reading rooms and study areas. The library also features an extensive archive detailing the history and evolution of modern medicine and organises a number of exhibitions every year. The Domus Medica has comfortable accommodation at competitive rates and the restaurant offers haute cuisine with a selection of excellent wines. There are additional club facilities with reciprocal international club arrangements. A number of awards are also offered to members of the society such as the Alan Emery prize, which is awarded to individuals in accredited training or research posts in the UK who publish a high quality research article in the field, and the Ellison-Cliffe Travelling Fellowship which is available to trainee members of the RSM.

For further information about membership, visit www.rsm.ac.uk/membership/joining.php

French translators needed

At Unique, the Rare Chromosome Disorder Support Group, we now have more than 150 disorder-specific information guides available for families and professionals. The guides cover a huge variety of conditions from the relatively common (such as 47,XYY) to the extremely rare (such as Ring 2). A number of our guides are translated into the main languages of Europe. Our guides are translated by a native speaker and reviewed by geneticist or medical professional. We are currently looking for someone to review a number of our guides that have been translated into French. We do stipulate that translators and reviewers are native speakers of the language they are translating into and have a background in genetics.

If you would like to translate or review one of our guides, please let us know. To view and read the guides, go to the Unique website at www.rarechromo.org and click on the information leaflets area of the home page.

Contact:  
Sarah Wynn  
sarah@rarechromo.org  
0203 211 1098
British Human Genetics Conference
17-19 September 2012
University of Warwick, UK

Scientific Programme

BSHG Lecture: “The new genomic world: Hypothesis-generating modes of basic and clinical research, and clinical care”
given by Prof Leslie G Biesecker (NIH, USA)

Carter Lecture: “tbc”
given by Prof Arnold Munnich (Paris, France)

Symposia:
Genomic Medicine - Challenges for the 21st Century - Prof Sir John Burn (Newcastle), Prof Patrick Maxwell (London),
Prof Theresa Marteau (London), Prof Peter Furness (Leicester)
Advances in Neurodegenerative Disease - Dr Michael Hayden (UBC, Canada), Dr Rhona Macleod (Manchester),
Prof Stuart Pickering-Brown (Manchester)
Clinical Developments in Pharmacogenetics - Prof Munir Pirmohamed (Liverpool), Dr Ron van Schaik (Erasmus, NL),
Prof Katherine Payne (Manchester)
Epigenetics, basic concept, recent advances and public health implications - Prof Marcus Pembrey (Bristol),
Dr Graham Burdge (Southampton), Dr Jonathan Mill (London)
Interpreting novel variants; making sense out of missense - Dr Simon Ramsden (Manchester), Prof Sean Tavtigian (Utah, USA),
Prof Steven Brenner (Berkeley, USA)
Infertility, genetics and assisted reproductive technologies - Prof Alan Handside (London), Mrs Jenny Dunlop (Manchester),
Mr James Lavford-Davies (London)
Clinical Relevance of copy number variation - Prof Dr Stefan Mundlos (Germany)
Practical research in Genetic Healthcare - Dr John Crolla (Salisbury), Dr Helen Firth (Cambridge), Mr Alistair Kent (London),
Dr Jackie Walling (Novato, USA)
Broadening the Role of Genetics in Medicine - Prof John Whittaker (Stevenage), Prof Chris Ponting (Oxford),
Prof Gilean McVean (Oxford)

Workshops:
Treatment of Genetic Disease with Stem Cell Technology - Prof Lior Gepstein (Israel), Prof Majlinda Lako (Newcastle), Dr
Sanjay Sinha (Cambridge)
CNVs and Cytogenomics - Prof Jan Dumanski (Sweden), Dr Jayne Hehir-Kwa (Nijmegen, The Netherlands)

Education:
Next Generation Sequencing / Bioinformatics - Issues in Cytogenetics - National Genetics Reference Laboratories
Assisting Genetic Specialists in their Educational Role - National Genetics Education and Development Centre

Debate: “This house believes that the art of clinical phenotyping is now redundant”
Prof Martin Bobrow (Cambridge), Prof Han Brunner (the Netherlands), Dr Richard Scott (London)
Plenary and concurrent sessions from submitted papers

Further Information from:
The Conference Office, British Society for Human Genetics, Clinical Genetics Unit, Birmingham Women’s Hospital, Edgbaston, Birmingham B15 2TG. Tel: +44 (0)121 627 2634 Fax: +44 (0)121 623 6971 Email: bshg@bshg.org.uk
Conference Website: www.bhgc.org.uk
Registered Charity
British Society for Human Genetics Annual General Meeting

Monday 17 September 2012 at 17:30 at the British Human Genetics Conference to be held at the University of Warwick

Agenda

1. Chairman’s Report
2. General Secretary’s Report
3. Treasurer’s Report
4. Conference Organiser’s Report
5. Any other business

If there are any matters which members wish to raise would they please send them to the General Secretary, Dr Chirag Patel, Clinical Genetics Unit, Birmingham Women’s Hospital, Edgbaston, Birmingham. B15 2TG by Monday 06 August 2012 email: chirag.patel@bwhct.nhs.uk

Welcome to New Members

31 new members were accepted by the British Society for Human Genetics in January 2012

Mr Edward Atack  ACC
Miss Emma Clark  ACC
Mr Aled Jones  ACC
Mrs Helen Bethell  AGNC
Miss Bethan Cowley  AGNC
Dr Deborah Holliday  AGNC
Ms Sibel Saya  AGNC
Mrs Annie Johnes  AGNC/CGG
Dr Mary Jones  AGNC/CGG
Dr Zakaria Eltahir  BSHG
Dr Kate Everett  BSHG
Dr Alison Foster  BSHG
Mr Gaurav Harlalka  BSHG
Dr Adam Rosenthal  CGG
Mrs Sofia Douzgou  CGS
Dr Elizabeth Forsythe  CGS
Dr Hannah Frost  CGS
Dr Jennifer Hague  CGS
Dr David Hunt  CGS
Dr Karen Low  CGS
Mr Sunil Bagha  CMGS
Miss Rebecca Beeveres  CMGS
Miss Naomi Bowers  CMGS
Mrs Kathryn Brammeier  CMGS
Dr Nicola Charlesworth  CMGS
Dr Hana Lango Allen  CMGS
Mrs Lorna Smith  CMGS
Miss Katrina Smith  CMGS
Dr Mohammed Ghanim  CMGS/CGG
Dr Stephanie Dyke  SGPPH
Miss Carol Smee  SGPPH

Travel awards

How to apply for Travel Awards

The Travel Award is for current members (who have been a member of the Society for at least one year) and for travel to overseas conferences, meetings, etc. There are NO travel awards available to attend UK based conferences, etc. It is highly unlikely that retrospective awards will be given.

Applications should be sent to Mrs Dina Kotecha, the Society’s Executive Officer in Birmingham with the applicants Date of Birth stated. There is no set form but please give as much information as possible and if you have submitted or had an abstract accepted please enclose a copy (it will be treated in strict confidence) indicating whether it is spoken or poster.

Priority will be given to young investigators presenting results at major meetings.

Applications should state the benefit to the applicant of receiving a travel award and clearly explain the part which the applicant played in the work. Another award cannot be granted to a successful applicant for three years. A small review committee has been formed to review applications for these awards. There are four DEADLINES a year for applications:

1 January  1 April
1 July  1 October

The successful applicant will be expected to write a report for the BSHG bulletin and may be asked to present the work at one of the Society’s meetings.
Conference reports

World congress for Huntington’s Disease
12th to 15th September
Melbourne, VIC, Australia

Nayana Lahiri, Clinical Genetics Registrar, SW Thames Regional Genetics Service, St. George’s University of London

I am very grateful to the BSHG for part funding my trip to Melbourne to attend the World Congress for Huntington’s Disease. The meeting was well worth the very long journey. The focus of the meeting was very much on how far HD research has come and looking forward to the real possibility of disease modifying clinical trials in the next few years. There were a number of excellent presentations on novel therapeutic approaches in HD. In particular, huntingtin lowering strategies in the form of anti-sense oligonucleotides and siRNA are nearing human trials. We also heard about immune dysregulation in HD and a Kynurenine 3-monooxygenase (KMO) inhibitor called JM6. This drug has been injected into the blood of mouse models of HD and resulted in symptomatic improvement and prolonged survival. This is a really exciting finding as one of the barriers to developing HD therapies has been the challenge of delivering drugs to the brain.

The collaborative spirit of the HD community was also celebrated. The delegates were a mixture of clinicians, scientist, lay organisations and family members. Plans for a worldwide HD observational study – Enroll-HD, to encompass existing European, American and Latin American studies were unveiled.

One session was devoted to updates to the predictive testing guidelines. These guidelines have not been updated for nearly 20 years. Our knowledge of HD has advanced with regard to reduced penetrance alleles, intermediate alleles, options for PGD and the possibility of participating in clinical research which should be incorporated in the current guidelines.

Forthcoming conferences

4th International Conference on Quantitative Genetics:
17-22 June 2012
Venue: Edinburgh International Conference Centre
Contact: icqg4@in-conference.org.uk
Website: www.icqg2012.org.uk

Multidisciplinary integrated approaches to understand evasion of host immune responses by pathogens: 20 June 2012
Venue: The Penridge Suite 470 Bowes Road London
Contact: Euroscicon
(www.euroscicon.com)
Website: www.regonline.co.uk/host2012

(ESHG) European Human Genetics Conference: 23-26 June 2012
Venue: Nürnberg Convention Center Ost, Nürnberg, Germany
Contact: eshg@medacad.org
Website: www.eshg.org/eshg2012

HEART UK 26th Annual Conference: Metabolic Syndrome, Obesity and Pre-Diabetes: 27-29 June 2012
Venue: Newcastle Civic Centre Barras Bridge
Contact: Natasha Dougall
(wheldonevents@btconnect.com)
Website: www.heartuk.org.uk

The genetics of sleep and sleep disorders: 03 July 2012
Venue: Royal Society of Medicine, 1 Wimpole Street, London
Contact: The Palliative care section of the Royal Society of medicine
(sleep.disorders@rsm.ac.uk)
Website: www.rsm.ac.uk/academ/slc03.php

Inducing and Breaking Tolerogenic Antigen-Presenting Cell Function:
Venue: The Penridge Suite 470 Bowes Road London
Contact: enquiries@euroscicon.com
Website: www.regonline.co.uk/apc2012

Driving Forward NHS Genetic Services: 11 July 2012
Venue: DoubleTree by Hilton Hotel, Manchester
Contact: SBK Healthcare (enquiries@sbk-healthcare.co.uk)
Website: www.sbk-healthcare.com/genetic-conference/driving-forward-nhs-genetic-services

Human Genetics Society of Australasia 36th Annual Scientific Meeting: 22-25 July 2012
Venue: National Convention Centre
Canberra, Australia
Contact: Human Genetics Society of Australasia WALDRONSMITH Management (hgsa@wsm.com.au)
Website: www.hgsaconference.com.au/

The Second International Genomics Conference "Genomics for healthcare and socio-economic progress": 12-14 September 2012
Venue: The Wales Gene Park, Cardiff University School of Medicine
Contact: Mrs Angela Burgess
(burgessam@cf.ac.uk)

World congress for Huntington’s Disease
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Nayana Lahiri, Clinical Genetics Registrar, SW Thames Regional Genetics Service, St. George’s University of London

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28 Ernst Klenk Symposium in Molecular Medicine "The Genomic Future of Medicine": 30 September-02 October 2012
Venue: Medical Faculty of the University of Cologne MTI-Building, Germany
Contact: Dr Debora Grosskopf-Kroicher - Scientific Coordinator CMMC (debora.grosskopf-kroicher@uni-koeln.de)
Website: www.zmmk.uni-koeln.de/content/klenk_symposium_2012/program/index_eng.html
(BSHG) British Human Genetics Conference: 17 - 19 September 2012
Venue: University of Warwick
Contact: Dina Kotecha (bshg@bshg.org.uk)
Website: www.bhgc.org.uk
Bioinformatics for genetic scientists: 2 – 4 October 2012
Venue: The Nowgen Centre, 29 Grafton Street, Manchester, M13 9WU
Cost: Public Sector £350 Private/Overseas £400 (Until 31 August); Public Sector £400 Private/Overseas £450 (From 1 September)
Contact: Tom Hancocks 0161 2765956 or training@nowgen.org.uk
Familial bowel cancer study day: 11 October 2012
Venue: The Nowgen Centre, 29 Grafton Street, Manchester, M13 9WU
Cost: UK Public Sector £195 Private/Overseas £250 (Until 30 June); Public Sector £250 Private/Overseas £375 (From 1 July)
Contact: Kate Mulryan 0161 2765956 or training@nowgen.org.uk
XXth World Congress of Psychiatric Genetics: Confronting the Complexity of Brain and Behavior: 14-18 October 2012
Venue: Congress Center Hamburg (CCH), Germany
Contact: Lyn Hopmayer (lhopmayer@schizophreniaresearchsociety.org)
Website: www.ispg.net
Bioinformatics for clinical geneticists: 16 – 17 October 2012
Venue: The Nowgen Centre, 29 Grafton Street, Manchester, M13 9WU
Cost: Public Sector £350 Private Sector £400 (Until 30 June); Public Sector £425 Private Sector £475 (From 1 July)
Contact: Tom Hancocks 0161 2765956 or training@nowgen.org.uk
Next generation sequencing bioinformatics: November 2012, Date to be confirmed
Venue: The Nowgen Centre, 29 Grafton Street, Manchester, M13 9WU
Cost: To be confirmed
Contact: Tom Hancocks 0161 2765956 or training@nowgen.org.uk
(ASHG) 62nd Annual Meeting of the American Society of Human Genetics: 06-10 November 2012
Venue: Moscone Center, 747 Howard Street, San Francisco
Contact: ASHG (ashgmeetings@ashg.org)
Website: www.ashg.org/2012meeting
New Frontiers in Personal Genomics: 03-04 December 2012
Venue: Radboud Auditorium, Geert Grootplein 15, 6525 GA Nijmegen
Contact: Nijmegen Centre for Molecular Life Sciences & Radboud University Nijmegen Medical Centre
Website: www.ncmls.eu/newfrontiers2012

BSHG News Editor

Deadline for contributions for next issue is 30 November 2012
BSHG Editor: Michelle Bishop PhD
NHS National Genetics Education and Development Centre
Morris House, Birmingham Women’s NHS Foundation Trust, Edgbaston, Birmingham B15 2TG
Tel: 0121 623 6975
Fax: 0121 623 6968
Email: Michelle.Bishop@geneticseducation.nhs.uk
Editorial

Result of the ACC ballot to dissolve the Association

Angela Douglas, ACC Chair and Simon McCullough, ACC Secretary

And now, we must bid you adieu. Hazel and I are laying down the reins of editorship for the final time. I'm off to seek my fortune in the rock’n’roll world of external quality assessment and Hazel for a well deserved rest.

Watching the inner machinations of our noble profession during such a transformative period has been a fascinating opportunity, for which we are both very grateful.

The leitmotif running through this issue is, once again, change; the somewhat macabre sounding Instrument of Dissolution has done its work and the ACC and CMGS have been consigned to history. From their ashes doth spring the Association for Clinical Genetic Science.

ACC Chair Angela Douglas provides a thought provoking piece on the achievements of the ACC and the challenges and opportunities that lie ahead and STP trainee Maha Younes gives a wonderful account of the Birmingham Genetics 2012 conference where our brave new world seems to be taking shape nicely.

Also in this issue, Eileen Roberts provides feedback on the recent FRCPath written examination and Polly Talley reports back from the UK Cancer Cytogenetics meeting in Newcastle.

Many thanks, as ever, to all of our contributors. We're rather slender this time around; if cytogenetics wants a voice within The Association for Clinical Genetic Science we need to make ourselves heard.

Stu

The result of the ACC vote on the Special resolution to approve the Instrument of Dissolution of the society is as follows:

Total number of ballots returned including proxy votes: 158

Number of ballot papers For dissolution including proxy votes: 153 (96.7%)

Number of ballot papers Against dissolution including proxy votes: 5 (3.3%)

The Special resolution was approved and ACC Council will be proceeding to dissolve the ACC and establish a new body with the CMGS. The members present at the AGM approved the new name of the society (as did the CMGS members at their AGM) which will be known as The Association for Clinical Genetic Science.
ACC Chairman’s Summary, review for period
April 2011 – March 2012

Angela Douglas Chairman of the ACC

This was a historic Annual General Meeting; it is likely to be the last AGM for the ACC, so take some time to review all that the ACC has achieved over the decades it has been in operation, how far we have come as a Profession and be proud to be a part of the Association for Clinical Cytogenetics.

This has been a very busy period with the release of several papers from the Department of Health (DH) for consultation, aligned to the White Paper, Liberating the NHS and the NHS reforms and Health Bill. It has also been an interesting time of budget reflections, reducing costs as part of the many QIPP programmes, culminating with the newly announced spending review in October 2011. Earlier this year the work carried out, by the Human Genomic Strategy Group (HGSG) and affiliated working groups, for government ministers, was brought together under the Department of Health’s publication Building on our Inheritance (January 2012).

The ACC as a body continued to grow in 2011-12, receiving applications from new aspiring members, like the ACC Council, they understand that being part of a body that has a strong representation across the wider healthcare agenda is vital to our sustainability and future success. In the past year, the Genetics Commissioning Advisory Group (GENCAG) was dissolved, the National Genetics Reference Laboratories (NGRL’s) lost their funding, the United Kingdom Genetics Testing Network (UKGTN) re-established its terms of reference, the Association for Clinical Scientists (ACS) came under threat, Modernising Science Careers (MSC) was launched in earnest and new players entered the arena in the form of the Academy for Healthcare Science and the National School for Healthcare Science (formerly the National School for Genetics Education).

We, as a body, made the decision to merge with the Clinical Molecular Genetic Society (CMGS) in order that both memberships will continue to grow and gain greater visibility and influence with these groups and others emerging. A joint body will provide both memberships with the stronger coherent voice that our professions will need to ensure our future sustainability and influence in this ever changing and resource constrained environment. With this in mind, this period also saw the Executive Committees of both the ACC and CMGS continue to work collectively to dissolve our respective bodies and bring the two memberships together under a single body that will be known as the “Association for Clinical Genetic Science – (AC(CCM)GS)”, a name chosen by the membership.

It has been an interesting year since I became Chair of the ACC; I have come to recognise even more how important and unique Cytogenetics is in healthcare. The work that we do spans every age from prenatal to old age and impacts on every medical specialty. The technology we use is constantly changing with the introduction over the decades of different ways of banding and looking at chromosomes, FISH, image analysis and now array technology.

We have become ‘Change Agents’, a skill that will be much sought after in the brave new world of the NHS, with Genomics our future and innovation and rapid technology adoption taking centre stage. I didn’t plan to become the Chair of the ACC, but I am proud to have represented the profession and all its members, and I am grateful to have been given the opportunity.
In late 18th century the arrival of steam power was the hero and the engine that began the Industrial Revolution and signalled fundamental change in major industry.

As members of the Lunar Society, scientists and inventors such as Erasmus Darwin, Matthew Boulton, James Watt, Joseph Priestley and Josiah Wedgwood would gather in Birmingham and engage in intellectual debate which was one of the driving forces behind the industrial revolution.

So, what better place than Birmingham - the city where the Society still exists - to hold the first fully integrated ACC/CMGS conference; a conference whose spirit was dynamic collaboration and innovation.

The conference paved the way for the impending merger of the ACC and the CMGS and focused around patient clinical pathways to steer the way for modern NHS genetics diagnostics.

The opening speech by Professor Andrew Read celebrated the 100 years of achievements of clinical laboratory genetics and took us on an inspirational journey reflecting on the past and the future of our profession. One prediction was that by 2020 we will be analysing the whole genome rather than selecting one gene or even one exome; as Professor Read put it, “do everything; analyze everything.”

Every day, the conference was packed with interesting talks and updates on services from across the country. There were dedicated sessions on molecular pathology, prenatal diagnosis, preimplantation diagnosis, developmental disorders, haematological malignancy, new technologies, services and bioinformatics.

As usual, I found it challenging to avoid clashes between interesting sessions. The posters were a great opportunity to get some valuable practical information on new services, diagnostic experience and technical issues.

With no doubt, the use of new technologies and innovations in diagnostic services was the central subject of this conference. Just a few years back personalised medicine with treatments tailored to patients’ individual genetic make up was just a futuristic idea. The update of phase one of CR-UK stratified medicine launched in 2011 made that idea a reality. The programme which is in its early stages is aiming to develop, by 2013, a scalable model and a national network for routine prospective molecular characterisation of tumours for NHS cancer patients.

One key point made was that the success of this programme, given its size and remit, is relying heavily on the regular communication and collaborations between the different participating clinical hubs and will lead to the use of automation and streamlined technologies. The panel gave very enthusiastic talks on the overview, workflow and the challenges of the programme and promisingly predicted its success “we think we are likely to succeed!” said one of the speakers.

Next generation sequencing (NGS) was the technology dominating with emphasis on using the technology to increase the repertoire of already existing services. Laboratories are either in the process of introducing the technology into their services or validating its use.

We were updated on the validation of NGS as a front-line test for patients with Familial Hypercholesterolemia and inherited peripheral neuropathies in Bristol, Retinitis Pigmentosa in Manchester and DNA repair and transcription disorders in children in Newcastle. In addition, non invasive prenatal tests using targeted and whole genome NGS have the potential to replace current Down syndrome screening tests with a test that would be diagnostic.

NGS is the way forward to develop a much more streamlined and comprehensive diagnostic services. The future is sequencing and with its predicted efficiency and cost, new areas of testing such as in complex diseases, pharmacogenetics and epigenetics will arise.

One interesting highlight for me was attending my first, and probably the last, general meetings of both the ACC and the CMGS. A milestone for the ACC was the vote to dissolve the current association and form a new body with colleagues from the CMGS. The members present at the AGM approved the new name of the society (as did the CMGS members at their AGM) which will be known as The Association for Clinical Genetic Science. The new body will have a newly elected chair and will be a charity, although this still seemed to be a matter of debate.

The Human Genomics Strategy Group report published in Jan 2012, highlights the UK’s achievements in genetics research to date and proposes a
strategic vision to realise the future benefit of genomics. Professor Sir John Burn spoke of the huge implications this report may have on us all in laboratory genetics. We have to keep up with the pace of changes in genomics medicine which will mean how we work constantly changing.

One criticism that Professor Burn had of the report was that there is no need to create yet another centralised genomic centre. We already have international genomic centres, such the Sanger institute, in addition to a well established regional clinical genetics units which are already working closely with other medical professions into bringing genomics revolutions closer to patients’ care; hence an infrastructure already exists. What we perhaps need to focus our energies on is on how we could best develop and resource our infrastructure. The main focus should be on translational medicine and improving translational research. Our main aim hence is to translate genetic science, or rather genomic science, into meaningful clinical results.

NGS is the steam engine that is revolutionising our genetics diagnostics services. It was very clear that whether you are a cytogeneticist or a molecular geneticist, the challenges we are facing are the same. We are going to be constantly under pressure to try and be flexible and up-to-date; to respond quickly to the ever changing technology platforms and the ever-changing landscape of genetics.

Array CGH boosts IVF success

A collaboration between the CARE Fertility Network and microarray manufacturers Bluegnome, has shown that pre implantation array CGH analysis of polar bodies removed from oocytes can triple the chance of the successful IVF whilst reducing the risk of multiple pregnancies.


Prenatal array study may lead to change in US guidelines

Researchers believe that the findings of a National Institute of Health funded study, contrasting the relative abilities of traditional karyotyping and microarrays to identify clinically relevant genetic abnormalities, are strong enough to force policy makers to make arrays the primary diagnostic tool in prenatal cases.

http://www.genomeweb.com//node/1032761?hq_e=el&hq_m=1203242&hq_l=1&hq_v=a8607b0960

Y Chromosome not disappearing

Suggestions that the most excellent of all chromosomes, the Y, could be on the verge of extinction were refuted in Nature in February. The attrition of genetic material from Y that has seen it reduced to carrying a mere 78 genes, a far cry from its heyday of over 800, appears to have halted. Professor Jennifer Hughes and her team at the Whitehead Institute in Cambridge Massachusetts compared the human Y to those of the chimpanzee and rhesus monkey and found there had been no significant loss in the last 600 million years.


Stress marks chromosomes

Exposure to repeated bullying or physical violence between the ages of 5 and 10 has been shown to significantly reduce telomere length, a study published in Molecular Psychiatry in April, has claimed. Telomere loss has been previously linked to ageing diseases such as diabetes and dementia.

http://www.bionews.org.uk/page_141973.asp
Feedback on the FRCPath Part 1 written examination 2012

Eileen Roberts, Bristol Genetics Laboratory

15 candidates sat the part 1 written examination in spring 2012. General problems across the two papers included poor time management - candidates are unlikely to pass unless they attempt an answer to four questions; and also failure to read the question thoroughly - several candidates gave answers that did not sufficiently address the requirements of the question or wasted time by giving information that, whilst not incorrect, did not answer the question.

Questions 1 and 2 on paper 1, and question 1 on paper 2, were common to molecular genetics and cytogenetics part 1 papers.

PAPER 1

1. Describe how uniparental disomy occurs, and using examples, explain how it can cause human disease.

All candidates answered this question. There were good answers that were well constructed and comprehensive from some candidates. Definitions of UPD were variable and often weak. The mechanism of how UPD is mediated was not required. Weaker candidates offered too few clinical examples. Segmental UPD and the unmasking of recessive mutations by isodisomy were often missed. A number of candidates mentioned a “battle of the sexes” which was neither part of the answer nor strictly accurate.

2. Discuss the use of next generation sequencing (NGS) and array technologies in a prenatal diagnostic setting.

Most candidates answered this question. Several candidates wasted time on describing in detail the current provision of prenatal diagnostic services, which was not required as part of this answer. Candidates tended to give too few examples from the literature of the use of these technologies in a prenatal setting and often showed a poor understanding of the technologies themselves (in particular NGS) and their applications.

3. Write short notes on the clinical phenotype and inheritance of FOUR of the following:
   a. 16p11.2 microdeletion syndrome
   b. 17q21.31 deletion
   c. 9q34 subtelomeric deletion
   d. 17p11.2p11.2 microduplication
   e. 22q11 microduplication
   f. 15q13.3 microdeletion

Only one candidate attempted this question and answered it well. With a choice of four from six options this was a straightforward question on which to pick marks up.

4. Describe the clinical features associated with Fanconi Anaemia (FA). Outline what is known about the genetic causes, and discuss methods for diagnostic testing for this condition.

All candidates answered this question. Some candidates answered this question well. Not all candidates accurately described the phenotypic variability of FA nor that progressive bone marrow failure is a cardinal feature of the disease. The question asked about diagnostic testing but several candidates failed to mention the role of molecular genetic testing in family follow up. Several candidates failed to mention that FA is an autosomal recessive condition with one rare X linked form. One or two candidates appeared to confuse FA with ataxia telangiectasia. Not all candidates were using the most relevant up to date information concerning for example FANCD and BRCA2.

5. Describe the aetiologies and clinical significance of commonly reported constitutional and acquired cytogenetic abnormalities involving chromosome 11.

All candidates answered this question. It was generally answered well. Weaker candidates failed to provide sufficient clinical examples of constitutional and acquired abnormalities of chromosome 11. Several candidates appeared confused with regards to causes of Beckwith Wiedemann syndrome. A number of candidates failed to specify that WAGR results from a deletion of 11p13. Several candidates included ataxia telangiectasia which is not strictly speaking an abnormality of chromosome 11 although the gene for this condition is located on chromosome 11.

PAPER 2

1. Describe with examples the benefits and challenges of implementing personalised medicine for cancer management.

Most candidates answered this question. This was not a question about next generation sequencing although several candidates appeared to think it was. Answers tended to be lacking in detail with too few examples of use in stratified medicine and failure to mention specific genetic markers used in stratification of patient groups. A clear distinction...
between personalised and stratified medicine was required. Costs of the ‘one drug fits all’ approach were not often considered. The need for large cohort studies e.g. Cancer Research UK was overlooked by some.

2. The purchasers of your laboratory genetic services have indicated that they are considering withdrawing funding support for karyotyping recurrent miscarriage patients. In your opinion is this decision appropriate? Discuss your response.

Most candidates answered this question. The answer to this question required a reasoned argument, backed up by appropriate evidence from the literature. Some candidates either failed to quote any evidence, or misquoted the evidence or the Royal College of Obstetricians and Gynaecologists guidelines (2011). Some proposed costly alternative strategies and/or failed to take any account of the costs of alternative strategies. Alternative strategies using molecular techniques were mentioned, but some candidates did not describe the benefits of these techniques over karyotyping.

3. What are the principles and practice of laboratory audit? How might audit be employed in a diagnostic genetics laboratory to review and improve practice?

Most candidates answered this question and it was generally well attempted. Weaker candidates failed to mention audit as an iterative and objective process measuring against defined standards. There was some confusion between vertical and horizontal audits. Some candidates simply described the different types of audit without commenting on how audit could be used to improve and review practice. A few candidates included audit data collected by NEQAS as an example of external audit which is no longer correct.

4. Write fully interpreted reports for the referring clinician based on the findings in EACH of the following cases:

   a. Neonate with karyotype 46,XY,del(10)(q26.1) in all cells examined

   b. A blood sample from a 3 year old girl with developmental delay with onset of frequent seizures; Karyotype: ish del(15)(q11.2;q11.2)(SNRPN-)

   c. arr 15q11.2q13.12(21,207,505-26,193,911)x1

   d. A prenatal chorionic villus sample referred for a combined risk of 1 in 75, previous QF-PCR analysis for the common trisomies showed a normal result. Cultured cells show a mosaic 47,XX,+2(47,XX,+2)[7]/46,XX karyotype [23]

   e. A referral from an elderly female, possible myeloproliferative neoplasm where genetic testing shows a positive result for a JAK2Val617Phe mutation and karyotype 46,XX, del(13)(q14)

Very few candidates attempted this question although it was a straightforward question on which to pick marks up. Weaknesses noted were the failure to assign specific clinical associations with the abnormalities noted; and incorrect assignment of the clinical significance of findings.

5. Write brief notes on a genetic testing strategy for THREE of the following:

   a. Acute myeloid leukaemia
   b. Chronic myeloid leukaemia
   c. Myeloproliferative neoplasms
   d. Non small cell lung cancer

Most candidates answered this question. Few wrote brief notes. Some candidates spent too much time describing the cytogenetic abnormalities associated with these diseases rather than the tests that are used. Several failed to mention the ACC Best Practice Guidelines for all the relevant diseases. A number of candidates failed to mention the role of genetic investigations at relapse. There were several errors in associating prognosis with specific genetic markers. Several candidates failed to mention the European LeukemiaNet guidelines for CML monitoring. The question required that molecular genetic testing was mentioned in addition to cytogenetic testing and a number of candidates failed to do this.
Report from the 34th UK Cancer Cytogenetics Group (UKCCG) meeting

Polly Talley

This year the UK Cancer Cytogenetics Group (UKCCG) are celebrating 20 years of the Cytogenetics Database and the programme at the 34th UKCCG meeting, held at the Medical School, Newcastle University on 22-23 March 2012, reflected this celebration. The programme covered some of the historical background to the UKCCG Database from the former director, Professor Lorna Secker-Walker, and the current director, Professor Christine Harrison, looked at current projects, trials and specific areas of interest. The programme then finished with a look to the future of diagnostic cancer genetics from Professor Mike Griffiths.

American guest lectures were given by Professors Nyla Heerema and Cheryl Willman MD and covered childhood leukaemia and issues of American regulation and research into high risk ALL. This caused a great stir, lots of interest and many conversations over drinks and then dinner sponsored by Oxford Gene Technology who are also celebrating their own 20 year anniversary this year.

Day two began with an overview of the current work from the Database by Professor Anthony Moorman, which is always extremely useful information to take back to the lab. Dr Robert Hills, chair of the AML17 trial data collection, shared his views of the modern day biomarkers in AML. He enthusiastically confirmed the importance of cytogenetics in this disease group – a great coup for us cytogeneticists! The Lymphoma Research European Guest Lecture was given by Professor Oskar Haas, who gave a very interesting take on the mysteries of leukaemia development in children.

All of the talks presented at the meeting were of an extremely high standard and there was great opportunity, with the meeting held over two days, for discussion with colleagues, both national and international. At the end of the two days we felt full of enthusiasm, with ideas for contribution and development in our laboratory. This meeting goes from strength to strength.

ACC News Editors

Deadline for contributions for next issue is 30 November 2012

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This year’s annual meeting of the Association of Genetic Nurses and Counsellors was held at the Cancer Research UK Cambridge Research Institute on the Addenbrooke’s Hospital site. The academic programme included papers and case studies from the membership in the morning and presentations on ophthalmology, dermatology and gastric cancer in the afternoon. The AGNC Annual General Meeting and Genetic Counsellor Registration Board Annual General Meeting were also scheduled as part of the day. Lunch was provided and there was time for poster viewing during breaks.

The first speaker was Dr Liz Ormondroyd (Oxford) who described the outcomes of a qualitative research study looking at how BRCA carrier status influences reproductive decision making. A selection of quotes illustrated how knowing about their BRCA status had influenced the participants’ thinking on having children and the use of prenatal diagnosis.

Sarah Smalley (Southampton) then presented an interesting case study highlighting the challenges which can arise when pre-implantation diagnosis is requested for mitochondrial disorders. This case described a couple whose previous child had died from Leigh disease. It was helpful to hear a summary of the PGD process for mitochondrial disorders. The presentation was particularly useful in showing the challenges of incorporating new technologies into prenatal genetic counselling practice.

The final talks from the membership gave an update on double heterozygosity in inherited cardiac conditions (Nicola Harper, Dublin) and the issues around predictive testing for individuals without capacity to give consent (Jennifer Wiggins, Surrey). Jennifer Wiggins presented a complex case which raised awareness of how we need to work differently when a patient has a learning disability. It also highlighted the importance of working together with staff from healthcare, education and social work organisations who are involved in their care as well as the wider family.

After lunch and poster viewing, an overview of genetics and ophthalmology was given by an expert in his field, Mr Martin Snead, Consultant Ophthalmic Surgeon at Addenbrooke’s Hospital. Mr Snead gave a very engaging presentation with a focus on his disease area of Stickler syndrome. It was useful to hear about how the UK Stickler syndrome diagnostic service operates and how sight loss associated with this condition can be prevented with prophylactic treatment.

Dr Nigel Burrows then gave a consultant dermatologist’s perspective on genetic skin disease, with lots of relevant clinical photographs. The remainder of the conference focussed on inherited gastric cancers. Dr Marc Tischkowitz, Honorary
Consultant in Genetics, talked about the various genetic and environmental triggers leading to the development of gastric cancer. He also gave a helpful overview of the hereditary cancer predisposition syndromes in which gastric cancer is a primary or associated feature. The final presentations provided lots of insight into the management of individuals at high increased risk of gastric cancer, including detailed information on screening, surgery and a patient’s experience. Dr Massimiliano Di Pietro, Honorary Consultant in Gastroenterology discussed the current approach to screening the stomach area using virtual chromoendoscopy. As an alternative to lifelong screening, some individuals with a confirmed high risk of stomach cancer opt to undergo risk reducing surgery and this process was explained by Mr Richard Hardwick, Specialist Upper Gastrointestinal Tract Surgeon. As well as learning about the surgical procedure, Mr Hardwick also presented a summary of the team’s data from their quality of life assessment, comparing patients’ wellbeing before and after gastrectomy. This sort of information is invaluable for genetic counsellors seeing individuals at high risk of gastric cancer who are making decisions about their management.

Sue Richardson talked about her busy role as Research Nurse in the Familial Gastric Cancer Study. We were then fortunate to hear about a patient’s experience of learning about her gastric cancer risk, undergoing predictive testing for CDH1 and risk reducing gastrectomy.

We had excellent IT support from the staff at Cambridge Research Institute and the well organised programme was carried off smoothly by the skills of the chairpersons from the Cambridge Genetics team. As a new recruit to this team I was not involved in the organisation, but can echo the overwhelmingly positive feedback from the membership provided on the evaluation forms that it was a very successful day.

Finally, congratulations to Flora Boyd and her group (Cardiff) who were awarded the poster prize of £50.
Profile of Nottingham Clinical Genetics Service

Marjie Miles, Nottingham

Setting up the department
The Nottingham service was set up in 1975 by Dr Fitzsimmons, a paediatrician with a particular interest in genetics and dysmorphology. Nottingham has since taken a particular interest in dysmorphology. In 1983 Penny Guilbert joined the team of three genetic nurse specialists. Dr Fitzsimmons was extremely supportive of developing the role of genetic nurse specialists and was keen to support their autonomy and responsibility. In 1988 Penny became the service lead for Nottingham and took on the chairmanship of the Genetic Nurse and Social Workers Association which later became the Association of Genetic Nurses and Counsellors (AGNC). She was instrumental in pushing forward regulation and specialist training for genetic nurses/counsellors.

Population
The service covers a population of 2.3 million and serves a mixture of urban and rural communities in Nottinghamshire, Southern Derbyshire, mid and southern Lincolnshire and northern Leicestershire. Our department is part of Nottingham University Hospitals NHS Trust, and in April 2010 we moved into a refurbished building, The Gables, on the City Campus which adjoins the genetics laboratories.

Staff
Currently we have five consultants who collectively work 4.5 wte:
- Dr Nora Shannon (current Clinical Lead)
- Dr Mohnish Suri
- Dr Ajoy Sarkar
- Dr Jacqueline Webb
- Dr Rachel Harrison

We have eleven genetic/nurse counsellors, who work a mixture of full and part time hours, equating to 9.8 wte:
- Helene Westmoreland, Principal Genetic Counsellor/Team Leader (Registered)
- Nicola Drury, Principal Genetic Counsellor (Registered)
- Marjie Miles (Registered)
- Janet Rezzougui
- Keri Oliver (Registered)
- Sara Pasalodos (Registered)
- Rebecca Collier (Registered)
- Kate May (Registered)
- Janine Bowes
- Marie-Ann O’Reilly
- Diane Norbury
- Ann Selby: Research Nurse for DDD project
- Melanie Doyle: British Heart Foundation Cardiac Genetics Nurse Specialist
- Vicky Sugden: Haemachromatosis Nurse Specialist

We are very well supported by an excellent administrative team including an administration manager, medical secretaries, a PA for the genetic counsellors, clinic coordinators and a support secretary.

Clinics
We hold generic clinics in Nottingham, Derby, Mansfield, Newark, Ripley, Lincoln, Grantham and Boston with the furthest located 65 miles away.

Specialist clinics
We are involved in a number of multidisciplinary clinics and these include:

- Skeletal dysplasia clinics
- NF2 clinics
- Joint clinics at the Child Development Clinic
- Cardiac clinics at the Trent Regional Cardiac Centre

Laboratories
The cytogenetics and DNA laboratories are located within The Gables and we have weekly meetings with the cytogeneticists to discuss urgent cases and monthly meetings with the molecular geneticists, usually with visiting speakers, for professional development.

The Role of the Genetic Counsellors
As in all departments, the role of the genetic counsellor has evolved and changed. For many years, the lead genetic counsellor was also the service lead but that post has now been split to form two posts: the administration manager and the team leader. All our new referrals are triaged daily by one of the principal genetic counsellors and the consultant on-call. Occasionally, some cases are brought straight to a clinic appointment, but usually we offer either a pre-clinic telephone call or an assessment clinic appointment with one of the genetic counsellors. As with many departments, we still offer home visits, but these are assessed on clinical need. The GCs are not disease specific but run geographically based case-loads. We continue to co-counsel in some Consultant led clinics but we also run our own independent clinics that include a
“In 1988 Penny became the service lead for Nottingham and took on the chairmanship of the Genetic Nurse and Social Workers Association which later became the Association of Genetic Nurses and Counsellors (AGNC)”

We have been able to offer our two trainee genetic counsellors substantive posts. We are fortunate to continue to have six weekly individual clinical supervision provided by a counselling psychologist who works external to our department. We also have group supervision two to three times each year.

All the genetic counsellors actively participate in journal club, audit and contribute to the teaching activities of the department including the relatively new MSc in Clinical Science - Genetics run in conjunction with the University of Nottingham. We try to maintain a high profile locally and nationally and regularly attend the Ethics of Clinical Practice meetings within the Trust. Nicky Drury was an active member of the Human Genetics Commission until it was disbanded in June 2012.

Genetic Counsellors Registration Board (GCRB) Update
Barbara Stayner, GCRB Chair, Oxford

AGM April 2012 Li Ka-Shing Centre, CRUK, Cambridge

The board were kindly invited by the AGNC to move our AGM date to the AGNC Spring Meeting to increase participation by registered genetic counsellors (RGCs) and other interested parties. As finances were previously presented in the September 2011 AGM and are available on the website, the board took this opportunity to ask members to vote on changes to the Articles of Association, and provided an update on our Terms of Reference (TOR) and professional activities. Changes to the Articles were accepted as proposed, and will be submitted to Companies House.

Minutes of the AGM will be posted on the GCRB website, along with the updated TOR in the About Us section. The board continue to work with other organisations, such as the International Genetic Counselling Credentialing Committee and the committee investigating the feasibility of a European registration system, as well as with UK groups such as the AGNC and the Joint Committee for Genetic Counsellor Regulation. The chair took questions from attendees, and as ever, welcomes queries by phone, email and letter. Finally, the board would like to formally thank the AGNC for this opportunity, and also to congratulate the genetic counsellors in Cambridge for their superb organisation of the AGNC Spring Meeting.

Sign-off Mentor (SOM) Training Day 27 April 2012, Guys Hospital London

Sixteen people attended the SOM Training Day on 27 April 2012, comprising a mixture of experienced and novice mentors. The training day was led by Sally Watts (GCRB Board Member). The Board had invited Caroline Benjamin as a co-facilitator as she has extensive experience of assessing and mentoring. The evaluation of the day showed that the attendees were able to build their confidence and understanding of the registration process to prepare them for the role of an SOM.
The early part of 2012 has been a busy time for the AGNC. In April the Cambridge team invited us all to their beautiful city for another wonderful AGNC Spring Meeting. A big thank you to Gaya Connolly, Felicity Wadrup, Vicki Wiles, Jacqueline Hodgkinson and all the team in Cambridge for all their hard work and dedication in planning the meeting and arranging such engaging speakers in the varied programme. Next year our two day Spring Meeting will be held in Durham on the 15 and 16 April 2013, so save the date.

Our distinguished leader, Mark, reaches the end of his office on the committee this September. Mark has truly worked tirelessly as Chair over the last two years and we’re sure the membership would like to join us in extending a huge thank you to Mark for his leadership. Mark will be continuing his work on the Joint Committee for Genetic Counsellor Regulation (JCGCR).

September will therefore see changes to the committee structure with the chair moving from Scotland to Wales, under the leadership of Carolyn Owen. Her number two will be Oonagh Claber as Vice Chair, while Anita Bruce will become our new Secretary. Following recent elections, we also welcomed Donna McBride as our newest committee member in September. Congratulations to Donna and our sincerest thanks to all the candidates who offered their time to the AGNC by standing for election to the Committee. The AGNC Committee would also like to welcome Sarah Wilcox, who has joined us as the co-opted trainee/new GC representative. Thank you also to Sally Yerbury (now Sally Monks) for her contribution to the AGNC in this position previously.

In October, the AGNC hosted a meeting of the lead GCs of all the UK regional genetic centres to discuss current issues of importance to the profession. As part of the meeting we were able to obtain accurate information about the GC workforce in Regional Genetics Centres (RGCs). While our biannual census provides some information about numbers of GCs at different stages of their career, and about working practices, data has been limited because only a proportion of GCs participate in the census. This census has enabled us to ascertain that there are 272 GCs working in RGCs in the UK, with considerably variability between different centres. It may be useful to repeat both the meeting and data collection in the future.

AGNC Committee and AGNC members continue to represent the AGNC on various committees’ groups and workshops (summarised in figure 1). In particular, Georgie Hall and Chris Patch formed part of the Human Genomic Strategy Group, which recently produced a report highlighting recommendations in response to genomic technology. The AGNC are also involved in redesigning and modernising the websites of the BSHG and constituent groups, and in discussions about changes to the organisational format of the BSHG. We will keep you informed of progress on these developments.

We have recently updated the AGNC career structure document, which was originally published in 2005. This document has been revised to reflect changes in the registration process and in regulation. It aims to support GCs, managers and service leaders in developing appropriate GC roles and career structure locally in these currently challenging times. The document may also assist the ongoing work around formal regulation of the GC profession in the UK.

Both the updated career structure and new guidance for travel award applications are now available on the AGNC website. We have allocated additional funds for travel awards each year and streamlined the application process to encourage members to apply for these. We appreciate that financial constraints throughout the NHS pose challenges for maximising educational opportunities at the current time, and are keen to support members’ professional development, particularly in a climate of such exciting technological advances.

We encourage feedback from you all, so please contact us if there are issues relating to the profession which you feel require our attention.

**Figure 1: AGNC Representatives**

- BSHG Council (Mark Longmuir)
- Joint Committee on Medical Genetics- RCP, RCPath, Department of Health, & BSHG (Mark Longmuir)
- U.K.GTN Clinical & Scientific Advisory Group (Mark Longmuir)
- JCGCR (Georgie Hall, Mark Longmuir, Chris Patch, Chris Barnes, Jan Moore, Jan Birch)
- National Clinical Reference Group for Medical Genetics (Oonagh Claber & Chris Patch)
- NIHR Genetics Specialty Group (Caroline Benjamin)
- CGS Clinical Governance Group (Margaret James & Jess Williams)
- RCP Standardised medical records workshop (Anita Bruce)
- RCP Joint decision making workshop (Laura Boyes)
- U.K GTN – Gene Dossier Working Group (Glen Brice)
- RAPID Steering committee (Laura Boyes)
- Website working group (Anita Bruce, Gilian Bromilow)
- Human Genomic Strategy Group
  - Service Development (Chris Patch)
  - Education, Engagement & Training (Georgie Hall)

**Representation**

- Human Genomic Strategy Group
- Website working group (Anita Bruce, Gilian Bromilow)
- RAPID Steering committee (Laura Boyes)
- Website working group (Anita Bruce, Gilian Bromilow)
A short update on genetic counsellor regulation

Georgina Hall, Manchester

Many genetic counsellors, leads, clinicians and managers are asking about regulation of genetic counsellors. As you know, the Health Professions Council accepted that genetic counsellors fulfilled the requirement for statutory regulation and made this recommendation to the Secretary of State for Health at the end of 2009. However the current government decided that statutory regulation will not be extended to new health professions and a new system of Quality Assured Voluntary Registration will be developed as a regulatory framework run by the CHRE (www.chre.org.uk) – Council for Healthcare Regulatory Excellence (renamed Professional Standards Authority in the Health and Social Care Bill).

The CHRE aims to change the culture of regulation systems in health and social care, recognising the partnership between agencies (employers, professionals, regulatory bodies) in the protection of the public. ‘Quality Assurance’ of Professional Registers will be a kite mark of standards and professional accountability. Within the NHS, the CHRE are working to ensure employment of health professionals on Quality Assured Registers through processes such as commissioning (Any Qualified Providers) and incentives such as indemnity insurance. The GCRB are confident our Register will meet the standards required by the CHRE, but the scheme is due to launch in November 2012 and it will be some time before we may know the success and impact of this new system for regulation.

The Health Professions Council (HPC) stand by their decision that statutory regulation should be provided for Genetic Counsellors. A recent Law Commission consultation (http://lawcommission.justice.gov.uk/consultations/healthcare.htm) includes a recommendation for extension of statutory regulation to new professions where appropriate. In addition, the Secretary of State recently announced statutory regulation for Public Health Specialists who have followed the same specialist training scheme as doctors, although the government have said this had already been agreed prior to the Command Paper.

In summary, this is a changing picture. The AGNC and GCRB have formed a joint committee (JCGCR) to continue working with the HPC and the CHRE to monitor and respond to this evolving process. We have the support from Genetic Alliance UK and many other organisations (including UKGTN) that have provided documents in support of regulation for genetic counsellors. Although the method of regulation for genetic counsellors remains uncertain, we are working to achieve the requirement that all genetic counsellors will have to be registered to practice in the NHS in order to maintain standards of education, training and competence for the protection of patients.

JCGCR members:
Georgina Hall, Christine Patch, Mark Longmuir, Jan Walford-Moore, Jan Birch, Chris Barnes, Buddug Cope (Genetic Alliance UK)

References
Editorial
Natalie Canham, KGC

A good study design is more important than a good analysis
Diana Eccles, Academic Vice President, CGS

This edition seems to be largely about wanderlust and research, which is an entertaining combination. Of course many of us recruit into overseas research, so our patients’ DNA at least succeeds in covering both aspects on a regular basis. The pieces mentioning Meena Bhat’s dysmorphology course particularly made me think. Meena, like many on the Indian Sub-Continent, is the only Clinical Geneticist in her department. Since Bangalore itself has an estimated population of over 8.5 million, and its state Karnataka houses at least 52 million people, this must produce an extraordinary amount of work.

International collaborations are always likely to be a valuable resource for research, learning and experience. Peter Turnpenny’s article rightly promotes increased interaction with those departments less well-supported than ours. It is also important to interact with our better-supported colleagues, and the joint Dutch-UK CGS/CGG meeting in Newcastle recently underlined this nicely.

Not everyone might be aware that there is a UK Travel Scholarship funded by CGS which is designed to contribute to UK based members’ travels overseas, either to spend time in another centre, or perhaps to present at a conference. It is open to all UK resident members, including Consultants, and is offered four times a year. Anyone who is interested should go to the CGS website and apply!

Meanwhile, Diana Eccles has invaluable advice for those thinking of setting up Clinical Research Trials. This is something which is likely to become more and more relevant, as, finally, more of our conditions become potentially treatable. It is conceivable that a treatment for a rare genetic disorder could eventually be suitable for a related multifactorial disease, so anyone who became knowledgeable in such an area could well find themselves eminently employable!

The importance of properly evaluating new therapeutic interventions has been understood for thousands of years. The Canon of Medicine is an ancient Persian text written by Avicenna in 1025 AD, in which the following observations are made about the effective testing of therapeutic drugs:

1. The drug must be free from any extraneous accidental quality.
2. It must be used on a simple, not a composite, disease.
3. The drug must be tested with two contrary types of diseases, because sometimes a drug cures one disease by its essential qualities and another by its accidental ones.
4. The quality of the drug must correspond to the strength of the disease. For example, there are some drugs whose heat is less than the coldness of certain diseases, so that they would have no effect on them.
5. The time of action must be observed, so that essence and accident are not confused.
6. The effect of the drug must be seen to occur constantly or in many cases, for if this did not happen, it was an accidental effect.
7. The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man.

The current UK law governing the conduct of clinical trials is the Medicines for Human Use (Clinical Trials) Regulations 2004 and came into force on 1 May 2004.

This brings me to where I have been hiding these past few years. In addition to my usual cancer genetics clinical work and my research programme, I have been the Director of the Southampton Clinical Trials Unit. So in my introductory communication as the new CGS Academic Vice President I am hoping to transfer some of my experiences of running a Clinical Trials Unit. If you are interested in developing treatments that make a difference to outcomes in your patients then consider broadening your experience by learning more about clinical trials. You can find more information about clinical trials on the website of the UK Clinical Research Collaboration (UKCRC) (http://www.ukcrc.org/infrastructure/ctu/).

Currently, training for clinical geneticists does not encompass any formal experience of clinical trials. Many trainees might recruit to studies and might be familiar with the Comprehensive Local Research Network (CLRN) currently chaired nationally for genetic disease by Professor Sir John Burn. The CLRN provides some infrastructure to facilitate the set-up of research studies provided they are on the national research portfolio. Recruitment of eligible people to studies of all types means ‘points’ for your Trust and points mean prizes (or in reality money which comes to the R&D office and gets handed to the CLRN to support more recruitment (roughly speaking)). You should also be familiar with Good Clinical Practice (have done the training) to recruit to trials. You should understand the question the study is asking. However maybe you have a question, you want to be the lead investigator, you want to get the funding and run the study and present
"Armed with a good question, a robust design and an idea of cost, you need to get funding"
“What is the key question you wish to address?”

original outline grant submission to signing a contract for funding the full study can take over a year.

So after all that, if you still fancy getting involved in running clinical trials:

What is the key question you wish to address? This can be harder to decide than you might think.

Is there clear therapeutic equipoise not only in the literature but amongst the clinical community expected to recruit? Presenting your study idea to a group of experts in the disease area is a good way of gauging the enthusiasm of your peers and finding out if someone has already thought of the same thing or something similar. If so, unless you are very powerful, there is no point competing, either join them or think of something else.

Why is the question important? You might think it is but you have to justify the importance to non-specialists - this is often a key aspect of trying to get funding for the study.

Who might be most interested in funding the study? The NIHR funding streams are worth exploring.

The Trial Development Group: who would be useful co-investigators, have you lined up a good statistician (or asked your local CTU or Research Design Service, RDS)?

Can you involve patient representatives? You should if appropriate not least because it can bring really valuable viewpoints and be helpful for example with developing information sheets and considering issues around feasibility. The NIHR funding streams absolutely expect the involvement of one or may lay members in the trials development group and even as co-applicants.

And finally for those of you who think clinical trials might be for you please explore the NIHR website and go and talk to your local CTU. There is now a specific funding stream for NIHR Clinical Trials Fellowships for trainees wanting to work with a CTU to gain experience of grant applications and the trials process. If you do have a trial idea and want to work it up there is no better way than to have some dedicated out of programme time and to work within a trials unit with all expertise on hand to work your idea into a funding application. Our first trainee joined the CTU in January this year. She has already submitted one outline trial proposal in April to an NIHR funding stream and is co-ordinating two more due in for the end of May deadline. She is a co-applicant on all three and if even one of the three is funded that will look very nice on her CV!

The first round of applications for this new funding stream opened in April 2012. Awards are 6 months in duration and will cover the full cost of employment and a contribution of up to £5,000 to support the clinical trial training activities of the fellowship. Applications must be a joint submission from the Trainee and Clinical Trials Unit. To find out more go to the website for the NIHR Trainee Coordinating Centre at http://www.nihrtcc.nhs.uk/ and check the newsflashes.
Indo-UK genetic meeting in Bangalore

Meena Bhat, Centre for Human Genetics, Bangalore

An intensive three day course on clinical dysmorphology titled “Genes and human development malformations” was conducted in Bangalore, India on 25 - 27 February 2012. The joint organizers of this course were Meenakshi Bhat (bhat.meena@gmail.com), Centre for Human Genetics (CHG), Bangalore and Dhavendra Kumar (kumard1@cardiff.ac.uk), University Hospital of Wales, Cardiff. A number of short courses in medical genetics have been conducted previously at the CHG funded by the department of Biotechnology (DBT), India.

This was the first meeting conducted in association with the recently convened Indo-UK Genetics Education forum. Over 80 participants, including clinical geneticists, scientists and other specialists from all over India, Sri Lanka and Iran attended. The topics discussed were genes and pathways in development of heart, CNS, hearing, bone, connective tissue and inborn metabolic disorders,

newer diagnostic tests and genetic counselling. The speakers from UK included Dhavendra Kumar, Peter Turnpenny, Jill Clayton-Smith, Ruth Newbury-Ecob, Andrew Jackson plus Bert de Vries from the Netherlands. The Indian speakers were IC Verma, Shubha Phadke, Madhulika Kabra, Ratna Puri, Arun Kumar, Anuranjan Anand, Girish Katta, Jayaram Kadandale and Meenakshi Bhat.

A clinical dysmorphology session for unknown cases was held on the last day with cases presented from seventeen centres in India. The third John Edwards lecture was delivered during the course of this meeting by Dr Peter Turnpenny (pictured with commemorative plaque) on NOTCH signalling and vertebral segmentation defects. Professor John Edwards was a personal friend of the CHG Director, Professor Sharat Chandra, and a well-wisher and teacher on various courses conducted in the past at the Centre for Human Genetics.
Letter from the President
Horizon scanning: CGS international work

Peter Turnpenny

A good training in medicine has, for a very long time, been something of a ‘licence to travel’. Wherever there are people there is disease, illness and huge opportunity for healthcare improvement. Medical migration takes many different forms: looking for a job, taking up a better job, and altruistically serving the underprivileged where few others want to venture. The NHS and allied medical research would not be the same without a great deal of talent that has migrated here from many places, and clinical genetics is no exception. There are also the globetrotting lecturers – I know someone who flew to a city in the far east, was collected at the airport and taken to the conference, gave his talk, then left the meeting to take the same aircraft back to the UK.

My route into genetics was far from conventional and I ‘caught the bug’ whilst working as a paediatrician in the Middle East for several years, in a place where it was normal for men to look for their life partners from among their own cousins and clan. On returning to the UK for a senior registrar post, I thought life might never be as interesting again, and even wondered if there was any appreciable genetic disease in Britain! Thankfully, I was quickly proved wrong on both counts but I have remained an internationalist and thoroughly enjoy cross-cultural exchanges. As a result, international work is an area that I have sought to promote within CGS. It is not that we do not travel enough, or have been backward in establishing global research collaborations – indeed, some have accrued large carbon footprints (I judge my own as modest by comparison). It’s just that more can be done to champion what we do beyond our shores, develop meaningful links with places less well off than ourselves, and broaden our own lifelong learning at the same time. The Beauchamp and Childress four principles of medical ethics are familiar to us but I have always thought the last one – ‘justice’ (basically, equitable distribution of healthcare) – has a particularly long course to run, especially from a global perspective.

Horror stories of (the lack of) maternal and child health are familiar to everybody but we, above all specialty groups, also know that genetic testing is beyond the reach and pocket of most of the world’s population. There are, of course, some grand international efforts underway, such as the Human Variome Project, successor to the Human Genome Project, which aims to populate the DNA databases of the world’s populations – a not inconsiderable task. But at some point the science has to be delivered to the patient/family who present with a clinical problem, which requires a competent professional. This reasoning lies behind the annual CGS International Scholarship, now in its fifth year and in a position to support two visitors from less well off places who work in relative isolation. The Council has also approved more funds for UK-based members to attend international conferences, teach, or acquire new skills, either in centres of excellence or developing situations.

In February it was a real privilege and great fun to help teach in Bangalore at a meeting organised by Meena Bhatt locally (formerly Guy’s Hospital) and Dhavendra Kumar (Cardiff) – a three-day Clinical Dysmorphology course: ‘Genes and Human Developmental Malformations’. This was not the first such event and hopefully not the last. Jill Clayton-Smith, Ruth Newbury-Ecob, Andrew Jackson, and Bert de Vries (Nijmegen) were part of the faculty, having negotiated some scary ‘visa application’ moments. We all spoke about our areas of special interest and there were some superb talks from local geneticists, including Ishwar Verma from Delhi (co-founder of clinical
Trainee column

Hannah Titheradge, Birmingham

I have now taken over from Rob Hastings as the new CGS trainee representative. I’m sure we are all grateful to Rob for all his work on our behalf. Meena continues as the second trainee representative.

It was lovely to catch up with many of you at the CGS Spring Meeting in Newcastle recently. Congratulations to Serena Nik-Zainal for winning the SpR presentation prize and to all the other registrars who presented, it made for a very interesting afternoon. Thank you as well to Anna Dubois and Brian Wilson for organising the registrar meal out in Newcastle. I believe a good time was had by all!

The main discussion point recently has been around the forthcoming Certificate of Medical Genetics examination. We have been informed that the first sitting in the Autumn will be held on Tuesday 25th September 2012. There will be centres in London, Sheffield, Edinburgh and Dublin. Application can be made shortly via the College of Pathologists website and will need to be submitted by Friday 6th July. The cost of the examination will be £510. The format will be a 3 hour paper consisting of 20 short answer questions, each worth a total of 20 marks. There are 5 example questions also on the College of Pathologists website, but sadly there will be no more practice questions released.

Earlier this year a few of the South West of Britain (SWOB) registrars wrote some practice examination questions. The exercise was very helpful and will be more powerful with more people involved. Rebecca Igboke (Birmingham) and I organised a meeting at the CGS conference to set up a virtual nationwide study group to extend this to other areas of the country. We were very pleased to see so many people at the meeting, keen to join our group. If there is anyone else who would like to join us, please feel free to contact me. Hopefully we will soon have a good bank of practice questions. Coming to a bookstore near you soon…!

Meena and I are keen to hear about any issues you would like raised nationally at the CGS council meetings. Please feel free to contact us on Hannah.titheradge@bwhct.nhs.uk, or meena.balasubramanian@sch.nhs.uk.

“I thought life might never be as interesting again”

Hannah Titheradge, Birmingham

genetics in India) and Shubha Phadke from Lucknow (the first CGS International Scholar in 2009). Bert, as well as giving more talks than anyone else – about all things “Nijmegen-ish” – kept us all amused with his constant banter. We all easily adapted to a totally native diet and kept very well. Whilst the others jetted off home I moved on to visit two genetic centres – firstly Lucknow, then Delhi. Finally, I took the first class (but inexpensive) train with Ishwar Verma to Chandigarh to speak at the Indian Society of Human Genetics meeting. Interestingly, this had a strong laboratory emphasis and very few clinical geneticists, who are forging their own professional organisation, attended. Could the developments in BSHG be of help to them? I met a wonderful lady at Chandigarh, Annie Hassan, who is passionate about developing genetic counselling but inevitably facing obstacles of Himalayan proportions. She has asked for help, to which I can only utter, “Help!”

Personally, I am indebted to Dhavendra for making things happen in various ways. The experience of crossing two big cities (not even in rush hour) left me feeling that the entire population of the world lives there. It does not, but obviously there are enormous numbers of patients, and only a handful of clinical geneticists. Hitherto, those trained locally have all done so through Shubha in Lucknow, and I was impressed by their knowledge and dysmorphology skills. Bert sprung various microdeletion syndromes on the unsuspecting audience and they were spot-on almost every time. I think we can learn from each other and a proposal for short-term trainee exchange programmes will come before the SAC in due course.

What’s not to like? With thought and care these can be win-win developments.
Minutes of Clinical Genetics Society AGM
15 March 2012, Centre for Life, Newcastle

Elisabeth Rosser, Secretary

The AGM was attended by 94 people.

These notes provide only a brief summary, details are available on request and on the website.

The Secretary, Elisabeth Rosser, presented a brief report.

The Treasurer, Amanda Collins presented the accounts, which were accepted by the meeting.

The Conference Organiser, Daniela Pilz presented a brief report. The 2013 meeting will be held at SOAS on March 14th.

The President, Peter Turnpenny, reviewed the work and achievements of the Society over the last year.

Thanks were expressed to Frances Flinter who is demitting office as Vice President and to retiring members of Council, Annie Procter and Kay Metcalfe. Thanks were also expressed to Daniela Pilz, Dina Kotecha and Eileen Connop for their organisation of the conference.
Dear Readers! This ever-so-slim edition of The Probe is brought to you courtesy of John Taylor whose piece on the ACC/CMGS Spring meeting is the sole contribution. How have we reached a point where the molecular contribution to the BSHG News comprises a single article? Is it apathy? Is it a fear of writing something that might be considered unacceptable? Or is it simply that no-one has time any more? I favour the latter explanation, having seen the generally frenetic pace of work of the average lab person. Actually, you only have to go as far as the lab audits to see that year-on-year sample numbers are up, report numbers are up and staff numbers are being pushed down. The pressure to deliver is far greater than it was twenty years ago; there is increasing competition from the private sector and even between laboratories. If we end up with the five regional labs allegedly demanded by the DH, then the remaining satellite labs will run on a much smaller scale, or not at all.

It is not surprising then, that people appear not to have time to write any more; this is also borne out by a dearth of publications from labs in the past few years. This is a trend that must be reversed! Yes, it is true that we are dedicated to delivering a service and no longer have the capacity to run the occasional research project on the side but we should harness the enthusiasm of the likes of John Taylor to record the experiences of using the new technologies. Individually and collectively, we are sitting on vast datasets which should be published and made available to colleagues in Europe and beyond. For example, it has become quite apparent in GWAS that patient cohorts need to be large enough to overcome statistical quirks, which enable six different studies of the same disease to give six different candidate genes.

So, dear readers, summon up your enthusiasm and let people know what you know!

Martin Schwarz
The ACC/CMGS spring conference: Was it a success?

John Taylor, Oxford Medical Genetics Laboratories, Oxford University Hospitals NHS Trust

How do you measure success? Is it an arbitrary scoring system on a questionnaire; a physical award providing self-gratification at a later date; or is it simply the ability to inspire and leave a lasting impression on others? For me, no means of assessment or prize would be able to reflect the degree of inspiration I gained from the recent ACC/CMGS conference. It is a nearly week since I attended the last presentation, yet the atmosphere and pace of scientific progress displayed at the joint ACC/CMGS spring conference still has my mind reeling. At a time when austerity measures imposed on the healthcare system could threaten to halt service development there has been an overwhelming response by the now joint ACGS society to demonstrate their commitment to patient care and the desire to provide a more comprehensive and cost effective means of genetic diagnosis.

It was remarkable to see that the recent acceleration in technology has enticed so many centres to embrace new sequencing platforms resulting in an unprecedented increase in the number of genes screened for several complex diseases. While the practicality of some of these screens and whether they can be successfully translated into a reliable and robust diagnostic service may be questioned, there can be no doubt as to the awe inspiring collective experience we have gained in such a short time. I could not help but imagine, in the absence of politics and competing markets, what could be achieved by us as a society. The collective value of such information and its translation into genetic data was epitomized in numerous presentations involving the DDD project and by guest speaker Joris Veltmann. Having seen the overwhelming advantage of large patient cohorts and data sets I now find myself championing, at least in principle, the idea of a centralised repository for genetic data; a notion proposed by Professor Sir John Burn in his address: Genetics, a changing landscape.

Amidst all the technological advancement, concerns over interpreting variants of unknown significance, and the need to provide quality assurance, it was wonderful to see that while we have one eye towards the blue sky another is firmly focused on patient care. Indeed the last session of the conference, quite literally gave voice to patients with infantile onset epilepsy after a genetic diagnosis and successful clinical follow up, in an excellent presentation by Rachel Ellis. After this final session I couldn’t help feel that while there is a scientific desire to screen more in an attempt to determine the aetiology of genetic disease we should not lose sight of what matters most and how this can be achieved through interdisciplinary cooperation with patients as the central focus.

How do you measure success? In less than a week I have been: inspired by several passionate guest speakers who have made me evaluate my own ethics regarding PGD testing; shown the power of emerging technologies on patient care; and the need for a more uniformed approach as our society progresses over then forthcoming years. I have seen but a snapshot of the potential each lab can provide to the healthcare system and the wealth of intellectual property housed within. Most of all I have experienced how passionate and dedicated clinical scientists can impact directly on other disciplines and influence the clinical outcome of patients. Such shared experiences have helped expand my education and galvanise my resolve to achieve more as a clinical scientist. For this, I would like to personally thank the speakers and organisers of this year’s spring meeting for a perfectly balanced conference and the ICC for a wonderful venue, which will be fondly remembered for many years to come.

CMGS News Editor
Deadline for contributions for next issue is 30 November 2012

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Editorial

Welcome to the latest edition of the Cancer Genetics Group Newsletter. Since our last edition changes to the CGG Steering Group have been finalised. We extend a warm welcome to Fiona Laloo who takes over as Chair from Anneke Lucassen. After nine years on the committee including three as Chair, Anneke will be standing down in 2013. We owe an enormous debt of gratitude to Anneke for her tireless commitment to the Steering Group. Other changes for 2012 see Lucy Side replacing Fiona as Secretary and three new members; Muna Ahmed, Dorothy Halliday and Adam Rosenthal. They replace Eamonn Sheridan, Lisa Jeffers and Nichola Bradshaw. Additionally, Katie Snape takes over from Anju Kilarni as SpR Rep. A warm welcome to the new committee members and our thanks to those now leaving.

In March we held our two-day spring conference at the Centre for Life in Newcastle. This year we were joined by the Clinical Genetics Society and also a strong contingent of Clinical Geneticists from The Netherlands. For those who couldn’t make it, Katie Snape summarises the highlights.

The American Association for Cancer Research (AACR) also had their annual conference in March. This year’s theme was ‘Accelerating Science: Concept to Clinic’. This reflects the rapidly growing synergies between basic, translational and clinical research, which are driving new strategies for cancer therapy and prevention. Emma Killick gives us a flavour of the key genetic and genomic moments. If you want more, download the AACR App with over 5700 abstracts at your fingertips!

Earlier this year the von Hippel-Lindau (VHL) Consortium held its 10th International Medical Symposium in Houston, Texas. Organised by MD Anderson and the VHL Family Alliance, this is a premiere event in VHL research and patient care. The conference sessions were rich and varied; from epigenetics to metabolomics to VHL patient engagement and support. Tabib Dabir presents a summary of his experiences.

Delivering high quality cancer care is increasingly influenced by modern genome technology. With the potential for vast quantities of data generation, this presents both challenges and opportunities for genetics services. In January’s Newsletter we heard how the cancer genetics team in Manchester is addressing these issues. This month, Alex Murray casts the spotlight on a different region. She reflects on the Cancer Genetics Service for Wales (CGSW). Since its launch in 1999 they have nurtured a strong clinical and basic science research base, which is now driving a growing emphasis on cancer therapeutics. Alex reveals how Wales is responding to the challenges facing clinical genetics. Through close involvement with the CRUK Stratified Medicine Programme and leading the new Cancer Genetics Biomedical Research Unit at Cardiff University, they are embracing and shaping cancer genetics in the 21st century.

Many of us have concerns over equality of access to genetics services. The Charity, Genetic Alliance UK is no exception. Recently they initiated a study to identify why people from minority ethnic groups seem less likely to access family cancer genetics services than the majority population. In London last February they ran a Familial Cancer Risk in Ethnic Minorities Workshop. They assembled an impressive array of stakeholders, underlining the degree of interest in this topic. Anna Allford summarises the proceedings and progress with the project so far. The hope is it will reveal ways in which clinical services can adapt and innovate to better serve our diverse, multi-ethnic communities.

Reducing cancer mortality is a fundamental objective of genetic medicine. Cancer screening in genetically predisposed individuals plays a vital role. National, evidence-based surveillance guidelines have helped deliver more consistent patient care in hereditary breast cancer. Similarly, in Lynch syndrome/HNPCC, colorectal cancer surveillance protocols are widely established. But for these families there are additional concerns over extra-colonic cancers, not least in the urinary tract. After gynaecological cancers this is the most frequently affected site. But without national guidelines there is likely to be regional variation in surveillance and access to services. Here Juliann Adlard and Alison Kraus consider the evidence for screening efficacy. They give some valuable insights and suggest that we should consider the scope for developing more consistent guidelines for the NHS.

We conclude this edition with the second in our series of ‘Ten Minutes with…’: In conversation with Nazneen Rahman, Professor of Human Genetics and Epidemiology at the Institute of Cancer Research, London. Naz tells why she got involved in genetic medicine in the first place and as someone frequently making groundbreaking news in research, she predicts where we may be heading!

Andrew Cuthbert (Deputy Editor)
Report from the Joint Meeting of the UK/Dutch Clinical Genetics Societies and Cancer Genetics Group

Katie Snape, Institute of Cancer Research, Sutton, Surrey

The Centre for Life in Newcastle was the chosen destination for the joint meeting of the UK/Dutch Clinical Genetics Societies and Cancer Genetics Group this year and the excited children running amok through the Life Science Centre served as a helpful reminder of how inspiring and stimulating science can be. The Thursday joint programme provided ample evidence for this, with optimistic talks on emerging therapies for genetic disorders, including interesting data on the immune response to DNA mismatch repair-deficient tumour cells (Magnus von Knebel Doeberitz, Heidelberg). Novel insights into growth and cancer were provided by, amongst others, the identification of mutations in the oncogene EZH2 in Weaver syndrome (Kate Tatton-Brown, London), and epigenetic modifications causing familial colorectal cancer (Megan Hitchens, Sydney). A further highlight came from the winner of the Robin Winter SpR Prize, Serena Nik-Zainal, who elegantly and amusingly described the application of bioinformatic methods to somatic whole genome sequencing data to identify breast cancer cell signatures, indicating germline predisposition through mutations in BRCA1 and BRCA2.

The Cancer Genetics Programme kicked off with the hip hop of Baba Brinkman ringing in our ears from the preceding night’s conference dinner, where we were regaled with the Rap Guide to Evolution (http://bababrinkman.bandcamp.com/album/the-rap-guide-to-evolution), telling us medicine, as that evolution, is about “Performance, Feedback, Revision”.

The first symposia delved comprehensively into the genetics of abdominal cancers, with thorough overviews of renal and pancreatic tumours, encompassing Birt-Hogg-Dubé syndrome, hereditary leiomyomatosis, renal cell carcinomas (Fred Menko, Amsterdam), Von Hippel-Lindau disease (Steve Ball, Newcastle), pancreatic neuroectodermal tumours (Juan Valle, Manchester) and pancreatic cancer (Mark Tischkowitz, Cambridge). The session had added flavour due to its cross-specialty nature, with endocrinologists, oncologists, and radiologists (Maria Sheridan, Leeds) joining geneticists in stepping up to the plate to give a broad context of the genetic and medical management of these conditions.

The post coffee discussion centred on screening guidelines for some of the above conditions, (renal carcinomas, paragangliomas and pancreatic cancers), with a précis of the protocols used by Dutch and UK groups. The lack of UK consensus across centres was noted, and a call for individuals willing to join a working group to standardise recommendations was made. The key point was that exponential increases in our knowledge of the underlying aetiology of genetic conditions and the expansive adoption of novel genetic and therapeutic technologies requires a fluid structure to protocols, with a requirement for regular review and revision (“Performance, Feedback, Revision”).

After lunch, an informative discussion of difficult cases was held, followed by an engaging talk by Michael Urban on the establishment of a breast cancer genetic service in the Western Cape Province of South Africa. This emphasised the effectiveness of a multi-disciplinary approach in a resource-deprived area, with genetics staff being primarily involved post testing for post-hoc counselling and cascade screening.

The final session presented novel research in cancer syndromes. Abstracts included a study of urological malignancies in Lynch syndrome that showed no association with bladder cancer, but a likely increased risk of prostate cancer in MSH2 mutation carriers (Paul Barrow, Cambridge). The effectiveness of a clinical roll-out of next generation sequencing to screen gene panels in renal cell carcinoma, phaeochromocytoma and paragangliomas (Eleanor Rattenberry, Birmingham), with the proviso that a protocol for the analysis and interpretation of variants of unknown significance is required in this setting and a study of isolated sebaceous skin tumours showing loss of MSH2/MSH6 gene expression which indicated that these individuals are unlikely to have an underlying genetic mutation in the absence of a personal or family history of Lynch syndrome (Lucy Side, London). As the sun set over the Tyne, the consensus appeared to be that an informative and entertaining time had been enjoyed by all present.
An update from the 2012 AACR Conference, Chicago

Emma Killick, Institute of Cancer Research, Sutton, Surrey

The 2012 annual American Association for Cancer Research (AACR) conference marked the end of Judy Garber’s presidential year. As such, her presidential address focussed on the developments in cancer genetics over the years she has worked in the field. She opened by quoting Nils Bohr “prediction is difficult, especially about the future” and went on to walk through the major achievements over the years, from the discovery of TP53 mutations in Li Fraumeni Syndrome using a candidate gene approach, to the use of genetic mutations in tumours to inform germline genetics such as the rare cases of germline EGFR mutations in hereditary lung cancer.

Moving on to how identification of cancer susceptibility genes can benefit patients, she discussed the difficulties posed by incomplete penetrance such as in pheochromocytoma. Three percent of people diagnosed with this tumour have a germline predisposition but often have no family history, supporting low penetrance in these cases. Professor Garber suggested that as our understanding of the biology of cancer developing in the context of genetic susceptibility increases, our screening and prophylactic measures should become more specific. For example, recent evidence shows that ovarian cancers in BRCA mutation carriers originate in the fimbrae of the fallopian tubes, which may allow for ovary-sparing prophylactic fallopian tube removal, thus avoiding the adverse effects of a premature menopause. She concluded by looking forward; as the cost of genotyping plummet and direct to consumer testing becomes more prevalent - will we reach a point in the future where every child has their genome read at birth?

Advances in Li Fraumeni syndrome were reviewed in two talks from David Malkin, Applying genomics to clinical surveillance and Novel mechanisms of tumour development in the TP53: Li-Fraumeni paradigm. He discussed the known modifiers of risk including MDM2 SNP 309 polymorphisms, measures of genetic instability - such as copy number variations and telomere length - gender, generation and environmental factors including smoking status, ionizing radiation and exposure to cytotoxic chemotherapy. Malkin proposed a process of tumour development whereby an individual inherits a mutation in TP53 which leads to accelerated telomere attrition and genetic instability which increases the likelihood of malignant transformation. Initially this may be low grade, but evidence points toward an increased tendency of lesions in people with Li Fraumeni Syndrome to undergo chromothripsis, a catastrophic event where hundreds to thousands of genomic rearrangements occur in a one-off cellular crisis. This model is supported by his surveillance study of TP53 mutation carriers in which individuals were offered a choice of the surveillance arm which consisted of a comprehensive clinical surveillance protocol including annual body and brain MRI, six monthly abdominal ultrasound and four monthly full blood count and biochemistry, or continuing their current management. Those in the surveillance arm were diagnosed with lower grade lesions and the survival was 100% versus 33% in the non-surveillance arm where individuals were diagnosed with more aggressive tumours, suggesting there is a window for early detection. Louise Strong’s meet-the-expert session Will the real Li-Fraumeni Syndrome please stand up again focussed on some of the known modifiers of risk, particularly general factors with evidence that anticipatory-like effects are seen in Li Fraumeni families. She also discussed the potential role of chromothripsis in tumour development.

Other cancer genetics highlights included Simon Gayther discussing the role of germline genetic mutations in BRCA1, BRCA2 and other genes involved in DNA repair in ovarian cancer, along with clinical implications in that BRCA mutation carriers with ovarian cancer have a better outcome than sporadic cases. Georgia Chenevix-Trench talked about genetic and environmental modifiers of risk in BRCA carriers. The overall message was that environmental risk factors were no different to sporadic cases with the caveat that studies are retrospective and small. Furthermore, BRCA1 and BRCA2 carriers tend to be analysed as one group. The consortium of investigators of modifiers of BRCA1/2 (CIMBA) initially concentrated on follow-up from GWAS carried out by OCAC and BCAC (the breast and ovarian cancer association consortia). However, it has now completed its own GWAS. There have been some differences in the SNPs associated with cancer risk in sporadic versus BRCA carriers. But once stratified by ER status, it appears that the differences are better explained by variation in subtype prevalence (ER negative cancers more common in BRCA1 carriers) rather than genotype.

In summary, one of the main threads throughout the cancer genetics seminars and the conference in its entirety was a focus on how developments in the laboratory can be used to make a real impact on patient care. Within cancer genetics this means personalised screening, targeted treatment and prophylactic measures where possible.
10th International von Hippel-Lindau (VHL) Symposium: A report from Houston, Texas

Tabib Dabir, Medical Genetics Department, Belfast City Hospital, Belfast

The 10th International VHL Medical Symposium, organized by the MD Anderson Cancer Centre (University of Texas) and the VHL Family Alliance took place at the Hotel ZaZa in Houston, Texas on January 26 to 29. It was meant to be the premiere international meeting providing a diverse and unique opportunity for attendees to share, discuss and learn the latest advancements in von Hippel-Lindau disease. I must say it did fulfil all these objectives, making my transatlantic trip a worthwhile experience. The VHL family forum is quite a proactive patient support group, managed by a group of dedicated people working tirelessly with the medical community to improve the quality of life for people affected by VHL. It was really a unique experience, interacting with patients, caregivers, researchers and medical professionals, all learning together to enhance the diagnosis and management of this multi-system disorder.

The first day of the meeting was dedicated to basic science and scientific advances, including sessions on VHL genomics and epigenetic regulation, cilia centrosome regulation, VHL proteostasis and VHL animal models. The Zebra fish model for VHL to test novel therapies was very impressive. The day had some excellent presentations highlighting the HIF pathway, the role of histone modifying genes, the aurora kinases and implications for new therapeutic opportunities. The main theme of the day was the ongoing research in the identification of key players in the molecular pathway of renal cancer and developing innovative strategies to restore VHL protein functionality. Ongoing research in modulators of TRic-VHL interaction and targeting Hsp70 to restore functionality of VHL protein seems to be a promising therapeutic option.

The second day of the meeting had individual sessions on endocrine, central nervous system, eye and renal manifestations in VHL. Each session had excellent presentations highlighting recent advances in medical and surgical management of VHL related tumours and the associated complications. There was truly an international flair to these sessions as various speakers from different parts of the world presented data related to patient outcomes, current care and management experiences at their centres.

The final day of the meeting was organised by VHL Family Alliance. The day started with a lay synopsis of the medical symposium for patients and their relatives. There were some interesting talks on finding appropriate medical care, engaging children and young adults in a safe discussion about VHL, and DNA testing. The interaction between patients, relatives, support groups and medical professionals was the highlight of the day. Surprisingly there was no abstract booklet provided and some of the oral presentations were also presented as posters at this meeting. However, this was richly compensated by the excellent organisation and very friendly atmosphere of the meeting (and they did provide an 8GB memory stick containing all the presentations at the end of the conference). The abstracts and talks from this meeting are also available at http://vhl.org/conf2012.

On a personal front this was quite a rich and satisfying experience. This was an inspirational meeting, providing me with a timely opportunity to interact with other likeminded health professionals from the UK and abroad. Unlike some centres in the UK, Belfast does not have a VHL clinic and screening arrangement for our VHL patients is far from satisfactory. My recent audit highlighted the need for a regional VHL clinic. I am delighted to announce that from June 2012 we will have our own VHL clinic.

VHL Family Alliance is celebrated this May ‘VHL awareness month’ and I think this report could be considered as my little contribution to it!
The Newsletter of the
British Society for Human Genetics
Issue 46  January 2012

The Cancer Genetics Service for Wales (CGSW) is part of the All Wales Medical Genetics Service (AWMGS). It was established in 1999 with funding from the National Assembly for Wales and support from Macmillan Cancer Relief, based on a model developed as part of a MRC funded trial of genetic services for breast cancer in Wales. Guidelines were drawn up with input from genetics, oncology, radiology and general practice to identify individuals at moderate or high risk, who would be eligible for referral. The service was led initially by Dr Jonathon Gray and a genetic counsellor, Liz France.

The CGSW now has three teams which are based close to the three cancer treatment centres in Wales. These are at the University Hospital of Wales in Cardiff, covering South East Wales, Singleton Hospital in Swansea covering South West and Mid Wales and Glan Clwyd Hospital in Rhyl, covering North Wales. Five consultants work as part of the service – Alex Murray, who is a full-time cancer geneticist and Emma McCann, Carrie Pottinger, Mark Rogers, and Julian Sampson who have mixed caseloads. Each team has a part-time associate specialist, several genetic counsellors and a family history coordinator. Five genetic counsellors work exclusively or predominantly within the cancer genetics service while the majority of the other counsellors see cancer cases as part of a mixed caseload.

Referrals to the service increased year on year from 1999 to 2007. Since then they have remained fairly stable at about 2500 per year. The majority of those seen have family histories of breast, ovarian and bowel cancer with smaller numbers of families referred for rarer, familial cancer syndromes. A significant proportion of patients receive their risk assessment information and advice by letter, rather than in clinic.

The CGSW works closely with research teams investigating basic and applied aspects of cancer genetics. The psychosocial research team evaluates the impact of genetic assessment and helps to develop models of service delivery that best meet patients’ information and support needs. In recent years the team has focused on patient involvement initiatives such as patient open days, patient panels and e-genetics. In 2010 they collected a series of digital patient stories and launched the Cancer Genetics StoryBank website: www.cancergeneticsstorybank.co.uk . The team also supports numerous genetic counselling MSc students, undertaking cancer genetics-related dissertation projects.

Basic and clinical research in the academic department of genetics includes projects on polyposis syndromes and renal tumours in tuberous sclerosis and is increasingly therapeutically focussed. There are major research links with oncology through pharmacogenetic projects on metastatic colorectal cancer and also the CRUK Stratified Medicine Programme, which has a technical hub based at the Institute of Medical Genetics.

In 2011 the Welsh Government funded a new Cancer Genetics Biomedical Research Unit at Cardiff University. The unit, which is led by the Institute of Medical Genetics, integrates genetic research across sporadic and hereditary cancers including haematological malignancies and solid tumours. This will facilitate translation of new genetic knowledge to better prevention, diagnosis and treatment of cancer.
Familial cancer risk in ethnic minorities workshop: The Wellcome Conference Centre, London, 20 February 2012

Anna Allford, Genetic Alliance UK, London

This half-day workshop brought together 41 participants including a wide range of stakeholders from diverse backgrounds to help develop and refine the findings of the study Familial cancer risk in ethnic minorities. The study is funded by the National Lottery through the Big Lottery Fund. The core study team include Anna Allford (Researcher) and Celine Lewis (Research Manager) from Genetic Alliance UK as well as academic partners Professor Joe Kai (Chief Investigator) and Professor Nadeem Qureshi (Division of Primary Care, University of Nottingham). The purpose of the study is twofold: to identify why people from minority ethnic groups with a significant family history of cancer are less likely to access clinical genetics services than the mainstream UK population and to inform the development of interventions in order to improve access to genetics services for people from minority ethnic groups.

People with, or at familial risk of breast, ovarian, colorectal, or prostate cancer who identified their ethnicity as Black Caribbean, South Asian or White Irish took part in interviews and focus groups. These common cancers were chosen because there are existing interventions. Also, healthcare professionals and key staff from two NHS sites were interviewed about providing cancer genetics services.

Jacquie Westwood, UKGTN Director, gave a presentation on Specialised Commissioning: the Challenge of Inequalities, detailing current guidelines and future developments that could help reduce variance and strengthen compliance to improve equality of access to cancer genetics services. Jacquie also outlined the responsibilities of service providers and Commissioners to ensure that quality standards are met.

Dr Julian Barwell, Senior Lecturer in Cancer Genetics and Honorary NHS Cancer Genetics Consultant, Leicester presented Referral Tipping Points; his results from a review of 508 referrals to Clinical Genetics in Leicester. Evidence shows people are being referred too late after a relative has died from cancer. Although this is not specific to ethnic minority patients his large sample does include ethnicity data. He has found that ethnic minority patients are referred to the cancer genetics service for different reasons than white majority patients.

What barriers to access were found in the study?
Barriers included the way in which families share or do not share information about inherited cancers. Some communities favour shared decision-making involving family, community elders or seeking religious guidance. Where English is not the first language this is a barrier. Stigma may also prevent minority ethnic patients from asking for medical advice. At the service level, triage using the Family History Questionnaire may prevent people from continuing with a referral if they cannot establish what medical conditions their relatives abroad had. Additionally, if they do gain access, non-directiveness in genetic counselling potentially leaves some ethnic minority patients with vague understanding of aspects of what the notion of family cancer means to them and their wider family. Furthermore, when we analysed the data, guidelines and pathways for referral appeared unclear and differ according to how they are interpreted by health care professionals. These and other issues were discussed in six facilitated groups during the afternoon.

What did the workshop participants have to say?
There was much agreement around the issues. This has helped verify and support the preliminary findings of the study. In addition, some very useful information and ideas were generated. Participants found sharing their experiences and areas of expertise added to their understanding, not only of potential barriers to access, but also how access for patients from minority ethnic communities could be facilitated. Crucially, raising awareness and mechanisms for support are called for together with increased vigilance by clinicians when cancers are diagnosed in younger patients (generally under 50). The event was very successful and many positive comments were received, confirming it had helped them to think about the issues. For a summary of the discussion and/or to send comments and feedback please contact Anna Allford at anna@geneticalliance.org.uk.
Urinary tract cancer screening in HNPCC - If, who, when, how?

Alison Kraus and Julian Adlard, Yorkshire Regional Genetics Service, Chapel Allerton Hospital, Leeds

Hereditary non-polyposis colorectal cancer (HNPCC) gene carriers have increased risks of cancers of the urinary tract, particularly of the ureter and renal pelvis, and to a lesser extent of the bladder and renal parenchyma. The average overall lifetime risk in published series is up to 12%.

**MSH2** mutations are associated with higher risks of urothelial cancers, with comparative series showing three to ten fold greater incidence relative to **MLH1**. **MSH6** mutation carriers appear to have low or intermediate risks, although confidence intervals of reported studies are wide. **PMS2** mutations appear to be associated with generally lower cancer penetrance than those in other mismatch repair genes. Deletions of the 3-prime end of the **EPCAM** gene, leading to tissue-specific silencing of **MLH2**, confer a predominantly colonic phenotype, though occasional urinary tract cancers have been reported.

Although urinary tract cancers associated with HNPPC occur on average at younger ages than sporadic cases, they are still rare under the age of 40 and are most common over the age of 50. The risk for men is two to three times that for women. Male **MSH2** carriers appear to have have the highest risk with one study estimating a 27% cumulative incidence to age 70.1

Questions remain regarding urinary tract screening in HNPPC. The most recent European/InSiGHT guidelines suggest one to two yearly surveillance from age 30-35 with abdominal ultrasound, urinalysis and cytology “if urinary tract cancer runs in the family”.3 Recommendations from US groups have also suggested urinary cytology beginning from age 25-35, accepting a low level of supporting evidence.4 Despite recommendations for urinary cytology, a Danish study has shown a sensitivity of only 29% for detecting asymptomatic urinary tract cancers using this modality.6 Greater sensitivity may be obtained when combined with urine dipstick or sedimentation to test for microhaematuria and with imaging modalities. Urinary markers of urothelial cancer are being investigated, for example the nuclear matrix protein-22 (NMP22), with simple testing kits being commercially available. Ultrasound may identify renal masses and urinary tract filling defects. Multidetector CT urography (MDCTU) is considered the gold standard for examination of the upper urinary tract and is widely available. However, the patient’s exposure to dye and irradiation needs to be considered and there are substantial costs. Flexible cystoscopy may be required to detect bladder cancers not identified by other modalities.

Cancer screening availability within the NHS is increasingly based on evidence and cost-effectiveness. There are no universally recognised recommendations for urinary tract screening within the UK, which has led to likely regional or sub-regional variation in practice. Further data collection and combination of retrospective or prospective series may give better estimates of potential risks and benefits.6 Ideally, a randomised study of different screening modalities would be conducted e.g. ‘simple’ screening such as urinalysis, versus more intensive screening including imaging and cystoscopy.

In the meantime, we should consider some screening for our patients, but previous guidelines would benefit from updating. Evidence for screening under the age of 40 appears to be weak, based on incidence rates alone, with some groups more recently suggesting starting at age 40+.1,2

There are balances to consider regarding the degree of screening, with a spectrum from urinalysis alone to cross-sectional imaging and cystoscopy. More intensive screening may be appropriate for the highest risk groups, such as **MSH2** carriers, particularly if male. New guidelines for the NHS (or Europe) would allow a basis for greater conformity and more reliable audit of outcomes. CGG would be well positioned to contribute to these.

**References**

Ten minutes with.......  
Nazneen Rahman

What excites you about cancer genetics?
I love the combination of gene discovery and clinical application. Most of our research questions and gene discoveries have resulted from patients we have seen in the clinic. Finding disease genes is like solving puzzles, very challenging, but that makes the successes all the sweeter. Being able to take them back into the clinic to help patients is incredibly rewarding.

What lead you to specialise in cancer genetics?
It was serendipitous really. I became pregnant when I was an SHO at the Marsden and decided that I wanted to do a period of research rather than be a registrar, primarily because I did not want to be on call at weekends! Mike Stratton was looking for a student so I went to work with him, a few months before he discovered BRCA2. It was extraordinarily exciting being in the lab at that time and I was immediately captivated by genetics. After I finished my PhD I decided to become a SpR in Genetics and because of my research it was natural for me to focus on cancer.

How do you see the role of cancer geneticists evolving in the future?
The new sequencing technologies are a game-changer both academically and clinically. As gene testing is now cheap and quick we no longer need to expend all our efforts trying to triage who has access to testing. We can now bring cancer gene testing into mainstream oncology and in due course, potentially, to the population generally. Of course there are huge challenges, and I think the experience of cancer geneticists will be invaluable.

What has been the highlight of your career so far?
When I started up my research team it was to work on childhood cancer genetics and overgrowth syndromes. When Mike Stratton moved to the Sanger Institute I took over the breast cancer genetics research. Quite early on in my career we found a gene, PALB2, which causes Fanconi anaemia and childhood cancer. As I was now doing breast cancer research as well I was able to show that it is also a breast cancer predisposition gene. We had two back-to-back papers in Nature Genetics and I was able to get programme funding for my research. It looked like I had been rather canny in researching into these two areas that then turned out to be linked, but it was actually chance!

How can we entice people to enter the field of cancer genetics in the future?
I think cancer genetics is going to be incredibly exciting over the next few years. I think we will be fending people off. Everyone will want to do it!

How do you see the role of leaders in cancer genetics / what do you think the role of leaders, such as yourself, in cancer genetics is?
I think a key role will be in communication and education, for clinicians, patients, policy-makers and the public. We have a wealth of experience and we need to make sure that it is used and we are heard.

How do you see the role of the cancer genetics steering group?
I think that the cancer genetics steering group will be increasingly important as we try to bring genetics into mainstream oncology and can act as a voice for cancer geneticists.
Erratum

Report from the Winter CGG Meeting, December 2011: UK FOCSS, UK Familial Ovarian Cancer Screening Study

It has been accepted that the following should replace the paragraphs printed in the CGG News, Issue 46 (page 54)

UK FOCSS started recruiting in 2002 and recruitment ended in 2010. Screening for the vast majority of women ended in June 2011. Women undergoing repeat testing for non-normal results were managed via the co-ordinating centre until the end of 2011, after which local gynaecologists took over management. All women will be followed up for a minimum of one year after their last screen on the study.

Dr Rosenthal reported unpublished results from phase 1 (annual screening) and preliminary results of phase 2 (4-monthly screening) of the study. Phase 1 results should be published shortly and Phase 2 results should be available in abstract form by the end of 2012, with publication anticipated in 2013. Whether the current surveillance protocol for ovarian carcinoma will ultimately lead to improved survival for these women remains to be seen. The NHS may defer a decision on whether or not to implement a national high-risk screening program until the general population screening results from the UKCTOCS trial become available in 2015.

Cancer Genetics training course

June 11-13th
This intensive residential course is set in the lovely grounds of Chilworth Manor near Southampton. Good air/rail links. See http://www.bw-chilworthmanor.co.uk/. This biennial event provides essential background and training for the aspiring (or perhaps rusty) health professional in cancer genetics. The course mixes lectures and small group discussions to cover all the essentials of cancer genetics. Faculty staff and guest speakers cover a broad range of topics suitable for doctors, nurses or genetic counsellors. All levels of training/expertise are welcomed. The course fee is £499 per person, including full board and lodging. 22 CPD Points applied for (RCP). Places are limited, so early booking is advised. The next course is not until 2014 in Manchester!

For a Programme and to book a place, please contact:

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Genethics Club
(www.genethicsclub.org)
Three meetings a year. The remaining date for 2012 is 17th October, London. 5 RCP approved CPD points per day. Come and discuss those difficult clinical cases or issues that you don’t have time to debate in detail in your own department. If you are interested in attending, or perhaps even hosting a Genethics club, please contact Michael Parker (michael.parker@ethox.ox.ac.uk) or Anneke Lucassen (a.m.lucassen@soton.ac.uk)

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Editorial

The climate of change we are experiencing in the NHS seems to be contagious. Our editor Tom Fowler has had to pass his role as SGPPH editor to me in order to fulfil obligations within the Health Service at governmental level. I’d like to take this opportunity to thank Tom for all his hard work and commitment to the SGPPH these last few years and wish him all the best for his future endeavours. He has left big shoes to fill.

I am delighted to introduce the articles for this issue of the SGPPH's contribution to the BSHG newsletter. Our featured articles consider patient benefit, communication of genetic risk and information and personalised and predictive medicine - issues with significant public health implications. These subjects are in keeping with our Spring Conference theme and the featured articles submitted by some of our speakers will share with you the importance and excitement of these fields.

Our first article addresses patient empowerment in clinical genetics services and touches on measuring patient benefits in order to evaluate clinical genetic practice and improve service delivery. Our next two articles discuss predictive genetic testing, parental responsibility and present exciting future research in communicating genetic risk information to children and families. The final articles discuss the case for personalised and predictive medicine – with an extremely insightful article addressing the economic value of the dynamic and evolving relationship between pharmaceuticals and diagnostics.

I do hope you enjoy reading this issue as much as I have had in collaborating with our authors and preparing it. I'd like to thank each of our authors for their excellent articles delivered within very tight deadlines!

I look forward to bringing you our next issue and would like to encourage all those interested in writing for us to please be in touch.

Dr Angelique Mavrodaris
Patient empowerment in clinical genetics services

Marion McAllister, Institute of Medical Genetics, Cardiff University

An enduring challenge in evaluating interventions in clinical genetics and genetic counselling is how best to measure patient benefits. A programme of research designed to address the problem of outcome measurement in clinical genetics was conducted in Manchester between 2003 and 2011. The first five years of this work was funded by the Department of Health at Nowgen, A Centre for Genetics in Healthcare, formerly the North West Genetics Knowledge Park. A systematic review, a Delphi survey and preliminary qualitative research identified six outcome domains as valued: Knowledge of the condition, quality of life, ability to cope, perceived personal control, decision-making, and accuracy of diagnosis. The qualitative element to this programme included interviews and focus groups conducted with 31 patients, 34 patient representatives, 24 health professionals and four service commissioners, and analysed using grounded theory. A model of empowerment was developed to summarise the patient benefits identified in the qualitative research. Empowerment enables a fulfilling family life, and emerged in this study as a belief system that reflects a person feeling in, or taking control of their lives and having responsibility or autonomy over decisions and choices, given the constraints imposed by the condition. Empowerment has five dimensions:

- **Cognitive control**: sense-making - understanding the condition, and what help and support is available; having an explanation for what has happened in the family.
- **Decisional control**: having some options for managing the condition/risk and able to make informed decisions between options.
- **Behavioural control**: able to do something to reduce harm or improve life for self child(ren) /at risk relatives/ descendents; able to make effective use of the health/social care systems for the benefit of the whole family.
- **Emotional regulation**: reflecting effective coping and adjustment.
- **Hope**: for a fulfilling family life, for oneself/relatives/future descendents.

When existing outcome measures identified in the systematic review were compared with the empowerment construct, it became clear that existing measures could not capture all important patient benefits. To address this, a follow-up study was funded by the Medical Research Council to develop a new Patient Reported Outcome Measure (PROM) to capture the five dimensions of empowerment. The Genetic Counselling Outcome Scale (GCOS-24) was tested with (a) 527 members of patient support groups for genetic conditions and (b) 241 patients attending clinical genetics services in Manchester, who completed the questionnaire before and after clinic attendance. These studies demonstrated that the GCOS-24 has good reliability, internal consistency, construct validity and sensitivity to change (Cohen’s d = 0.70).

The GCOS-24 therefore has good potential for use as a PROM to evaluate clinical genetics and genetic counselling interventions in both research and clinical contexts. Work is underway to explore the usefulness of the GCOS-24 to evaluate (i) clinical genetics practice in Cardiff and in four clinical genetics units in London and (ii) a new model of service delivery for inherited conditions as part of a programme of research funded by Fight for Sight and led by Prof Graeme Black in Manchester.
Families and professionals: the case of predictive genetic testing of children for adult onset conditions

Ingrid Holme, University of Southampton

In what situations should children be tested for adult onset conditions at the request of their parents? In 2010 Professor Anneke Lucassen and colleagues at the University of Southampton, Faculty of Medicine were awarded a 30 month project grant to fund research on this question. Dr Ingrid Holme was appointed as the Senior Research Fellow to explore the views of parents, young people and health care professionals about predictive genetic testing during childhood and the current professional guidelines. Dr Holme’s work draws upon 45 semi-structured interviews to explore the tensions between professionals adhering to professional guidelines, parents seeking to be responsible decision makers in the family and the ethos of personalised medicine.

UK professional guidelines, updated by the BSGH in 2010, state that predictive genetic testing for adult onset conditions should generally be delayed unless the result would affect the medical management of that child or until a child can make a decision for themselves. However, the guidance also describes circumstances in which it might be appropriate to proceed with testing and case studies in the guidance provide worked examples. Our research indicates that few professionals interviewed in this project have read the guidance and tend to believe that guidance prohibits such testing. Consequently the majority of professionals aim to deflect and delay requests from parents. At the annual CGS/CGG conference in March this year we presented data demonstrating how professionals direct parents’ decisions in this area. This includes using a number of steering tools such as reflecting back the request using negative language and bringing the parent(s) back for further discussion appointments. Professionals often experience organisational issues which impact upon the provision of genetic medicine, for example, the demise of home visits to explore such issues and fewer resources for follow up.

Our research indicates that parents talk to genetic services about predictive genetic testing of their children for a wide range of reasons, and many argue it is their parental responsibility and part of being a parent in today’s world. Initial analysis indicates this sense of parental responsibility connects with the parent’s own experience of having the predictive genetic test promoted as a positive empowering tool. This parental responsibility includes on-going communication with the child about their genetic inheritance; however for many in our study the specifics of the drip fed information depends on the genetic status of the child. As a result many feel hampered in performing their parental role by the lack of willingness of professionals to carry out the predictive genetic test. As will be further explored by Dr Holme, these tensions have important implications for how personalised medicine is realised within the family context.
Sharing information with children and young people about genetic risk: Using evidence to develop services for parents and practitioners

Karen Keenan, Health Services Research Unit, University of Aberdeen

This project, which aims to understand how information with children and young people about adult-onset genetic risk is shared to improve services, was developed by Dr Karen Keenan and her mentors Professor Lorna McKee and Dr Zosia Miedzybrodzka. The work is based on the findings of Dr Keenan’s PhD work and five years practical experience of working with individuals and families affected by Huntington’s disease (HD). Whilst Dr Keenan and her colleagues have had a longstanding interest in undertaking research into family communication about genetic risk, Dr Keenan’s experience as Youth Service Manager for the Scottish Huntington’s Association brought into sharp focus the complexities of sharing information about serious inherited conditions in families, and the extent to which there remains professional uncertainty about ‘what to tell children’. Whilst the team’s previous research with young people growing up at risk of HD found that children and young people do worry about their risk and have questions about genetic testing, it did not explore young people’s changing information needs in the transition from childhood to adulthood, important in a range of adult-onset genetic conditions, nor genetics professionals’ experiences of counselling at risk young people.

As such the aims of this study are to: explore the changing information needs of young people at risk of serious adult-onset inherited conditions; explore professional interactions with these young people and their parents; and further explore the impact of different parenting styles and modes of communication upon children and young people. In order to address these aims two adult-onset inherited disorders with different implications for parents and children were chosen: Huntington’s disease and Familial Hypercholesterolaemia. It is expected that the data will reveal differences in parent’s disclosure dilemmas and young people’s anxiety about hereditary risk, generating more evidence about a range of individual and family experiences.

In addition to a core research team the project also benefits from a wider advisory group of professionals and family members, all of whom bring experience, insight and a strong commitment to this sensitive and challenging area.

The overall aim of the project is to contribute needed evidence about what professionals and families should tell children and young people about adult-onset genetic risk. In the long term we hope this will lead to an improvement in the lives of those who grow up at risk of such serious inherited conditions.

The fellowship is a joint position within the Health Services Research Unit and Medical Genetics Group at the University of Aberdeen. For further information contact Karen by phone on 01224 438161 or email at: k.keenan@abdn.ac.uk

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References:


Personalised medicine – can common disorders learn from rare disease?

Pauline McCormack, Policy, Ethics and Life Sciences (PEALS) Research Centre, Newcastle University

If the 2009 BBC headline, an Era of personalised medicine awaits, is to be realised, there are a number of ethical and resource questions which will need to be discussed before personalised medicines can truly become a reality. Many of these issues are being dealt with in the rare disease community, where therapies which target sub-sets of patients with different genetic mutations are currently in development.

Take the case of Duchenne Muscular Dystrophy (DMD) – one of the more common rare diseases. An X-linked condition affecting 1 in 3,5000 live male births in the UK, it is progressive, relentless, chronically disabling and life limiting. DMD is caused by various mutations in the dystrophin gene which is responsible for building muscle. It is also the largest gene in the body made up of 79 exons (the segments of DNA which encode for mRNA) and DMD-causing mutations are found in lots of different exons. Trials are currently underway with a therapy called exon skipping which works by patching the mutation, thereby allowing production of a functional gene. Treatment must be targeted to the specific exon which is at fault and each one therefore requires a different exon skipping chemistry – perhaps up to 30 different chemistries will need to be developed to treat everyone with DMD.

The possibilities of exon skipping led myself and colleagues to ask a number of questions, most of which could be framed around the idea of justice. If a disease is made up of several subsets of patients, diagnosed genetically, how do we decide which subset to develop medicines for first? The most common group? The group where the medicine is easier to develop? The group where a wealthy individual finances the drug development?

The group who reside in a country where the health system has promised to pay for the therapy?

The last two questions bring us on to the on-going and often controversial question of health resources - if more medicines have to be developed and for smaller groups of patients, will they, by default, be more expensive than drugs made for large numbers? Are we looking at an exponentially rising pharmaceutical bill for healthcare systems? Will some countries or, in the UK, some GP consortia simply refuse to pay, as was the initial case with the breast cancer drug, Herceptin (http://news.bbc.co.uk/1/hi/health/4902150.stm)?

The availability to patients, of therapies for rare disease is already an issue despite an EU directive stating “patients suffering from rare conditions should be entitled to the same quality of treatment as other patients” (EU 141/2000). A 2010 survey by the rare disease patient umbrella group EURORDIS found that in some EU countries, only a third of rare disease drugs on the market were available to patients (http://www.eurordis.org/content/survey-patients%E2%80%99-access-orphan-drugs-europe).

If the move towards personalised medicine and genetic diagnosis means that one day there will be no such thing as common disease, the concerns the rare disease community have now might one day be concerns for all of us.
The economic value of companion diagnostics and stratified medicines to healthcare systems

Edward D Blair, Integrated Medicines Ltd, Cambridge UK

The development and commercialisation of stratified medicines in the UK and elsewhere requires a whole new appreciation of the economic value of the relationship between pharmaceutical companies and medical diagnostic companies. This economic valuation also impacts on other healthcare stakeholders as it influences pricing, payment and evaluation of technologies for both clinical- and cost-effectiveness. The clinical-effectiveness of stratified medicines also impacts on patients’ and clinicians’ education as it is important that these key stakeholders are able to recognise the benefits of selective treatment.

For many years, pharmaceutical companies have struggled with declining productivity, increasing development costs and attrition of traditional blockbuster medicines. Stratified medicines offer a solution to these three ills, while also offering considerable benefits in terms of patient outcomes. The use of biomarkers to identify patients in clinical studies has been shown to both reduce the size and duration of clinical studies, with considerable development cost benefits. The transition of biomarkers to validated indicators of clinical outcome, in the form of approved companion diagnostics, can improve market uptake, market size and market share in such a way that blockbuster revenues are retained. In addition, there is also evidence that companion diagnostics can protect proprietary medicines from generics late in the product lifecycle. Economic quantitation of these benefits over a 20 year period, from drug development through to life cycle management, suggests a potential net present value (NPV) uplift of $1.8bn, from $900M to $2.7bn. Furthermore, the apportionment of the NPV uplift between the pharma partner (Rx) and the diagnostic partner (Dx), based on the approximate scales of the business (Rx $1000bn, relevant Dx $10bn sales per annum) is probably not representative of the value contribution that the diagnostic test makes to the drug lifecycle. Thus, we have used value-modelling to look at how simple fee-for-service relationships between Rx and Dx might translate to risk-sharing relationships (the probability of success of a pharmaceutical is less 1-in-60, for a diagnostic it is more than 1-in-5, so the Dx partner might expect pharma sales royalty, or some hybrid of fee-for-service with reduced risk sharing. The structure of these relationships is guided by associating an Rx Product Profile with a Dx Product Profile, with the latter articulating the technical, clinical and commercial performance of a test that will ensure successful development of a linked stratified medicine.

Of course, establishing the true value of a stratified medicine-companion diagnostic relationship (SRx + CDx) then leads to some sense of pricing options, payer relationships and eventually reimbursement strategies, so the ‘simple’ Rx-Dx relationship has implications for all healthcare stakeholders. Indeed, there are cases of pay-for-performance that might be enhanced by companion diagnostics, and recent cases in oncology point to rapid assessment and approval by the US Food and Drug Administration. More timely access to effective therapies moves healthcare towards an era of predictive medicine, as opposed to reactive medicine, with the undoubted benefits of earlier treatment and better outcomes. In this respect, it may well be feasible to prolong life, but the challenge of future healthcare is to ensure that quality of life is commensurate with length of life.

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