Welcome to the 50th issue of BSGM News. This issue provides an update on the many exciting research projects that are currently being undertaken in clinical genetics. While the emerging knowledge and technologies are sure to enhance clinical practice (and fascinating to read for someone whose main source of intellectual stimulation has been Peppa Pig while on maternity leave), these projects highlight the many challenges that are faced when translating research findings into clinical practice. This issue also sees a large number of articles which have been submitted under the service development banner – a section that will now be a regular feature of BSGM News.

Unfortunately we have lost a sub section in this issue due to the dissolution of the Society for Genomic Policy and Population Health (SGPPH). For members of BSGM who have an interest in this area, I draw your attention to page 10 where Philippa Brice discusses the launch of PHG Exchange which will provide a platform for people who share an interest in genomics, policy and population health.

I would like to take this opportunity to thank Ann Kershaw, one of the editorial team for this newsletter, who retired from clinical practice at the end of January. Ann has been a constant source of support since I started as editor of this Newsletter and I wish her many happy days in her retirement.

I hope you enjoy reading this issue as much as I have enjoyed putting it together – it has been a welcome relief from nappy duty!

Michelle Bishop

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Let me start by wishing you all a very Happy New Year, I hope your New Year has started as you intended it to and you have managed to stick to your resolutions whatever they were. This year I am not breaking any resolutions, only because I didn’t set any, so one less thing to worry about.

Last year was a momentous one for the profession, what with a new NHS Commissioning board for England (NHS E), a new Specialised Commissioning framework and the introduction of the Medical Genetics Advisory Group; we have started to see a whole new way of working beginning to emerge around commissioning specialised services in the NHS. We have all also been concerned with the reconfiguration of Genetic Laboratory Services and more recently with the publication of the consultation document for the five year strategy for Specialised Commissioned Services, we have come to realise that all 143 Specialised Services are facing the same concerns. We are therefore being more proactive, as the experts in the field of Medical Genetics, in articulating what we believe are the guiding principles for reconfiguring Genetic Laboratory Services. We really need to decide though if we are going to present a more united professional standing across Regional Genetic Services of ‘Solidarity’ or are we going to continue the decline into ‘Subsidiarity’ and risk the unintended consequences of having to compete with each other as well as any other qualified provider. We have also seen the launch of the 100K Genome project. This project is putting the United Kingdom at the forefront of using whole genome sequencing for patient benefit and is going to have a profound long-term impact on services delivered on the front-line of the National Health Service (NHS). Therefore, we have ensured we are key stakeholders in driving that project forward with Genomics England (GeL) and have been heartened at every meeting with Professor Mark Caulfield (Lead Scientist for GeL) and at every news publication, that Mark is keeping the best interests on the Regional Genetic Services at the forefront of delivering this project. Professor Caulfield said at a recent meeting of Heads of Genetic Laboratory Services that he has no wish to destabilise the current NHS provision of Services and will work with the Regional Genetic Services to ensure the success of the programme through the engagement of the Regional services (to find out more follow the link: http://www.genomicsengland.co.uk/news/professor-mark-caulfield/)

We have also seen the publication of the Rare Diseases Strategy, which is heavily featured in the Specialised Commissioning five year Strategy, so again, more opportunities to influence as a profession. We have also started to debate the merits of a Rare Disease Registry(ies) and the benefit these will have for patients and clinicians, especially with the positive benefits to the NHS and patients evidenced from other registries, such as the Cancer Register. We will need to think through how we would want these to be delivered, do we create something new and bespoke, do we use the Orphanet framework or some other EU funded Genetic Registry(ies). In all of this we need to consider the cost to the NHS against a back drop of decreasing funding.

We are all facing the challenges of continuous requests year on year of cost
Non-invasive prenatal diagnosis update

Lyn Chitty on behalf of the RAPID team

Genetics and Genomic Medicine, UCL Institute of Child Health and Great Ormond Street Hospital for Children NHS Foundation Trust

Improvement programmes (CIP), is it time we started to work together to see if there are areas where we can make improvements to our costs through national procurement or nationally managed maintenance contracts? Or even just sharing good CIP ideas across services – What have you managed to save money on that could also be implemented in other regions. From what we have heard the financial constraints are not going to get any better until at least 2017, we cannot go on working the way we have in the past and all survive till then, so how do we work better together to ensure the sustainability of NHS Genetic Services in the next three years?

Finally, seven day working, another aspiration of NHS E and Sir Bruce Keogh. How are we going to engage in this debate? If all other Clinical Services move to seven day working then the public and NHS E will expect us to do the same - do we need to start to debate this?

I leave you with all these questions and thoughts, and again wish you all an innovative and thought provoking new year as well as a happy one.

RAPID is a five year NIHR funded programme grant for applied research that aims to improve the quality of NHS prenatal diagnostic services by evaluating early non-invasive prenatal diagnosis or testing (NIPD/T) based on cell free (cf) DNA in maternal plasma. Note the change in nomenclature from the last update when we discussed cell free fetal (cff) DNA as we need to be aware that we are testing the maternal as well as the fetal DNA when offering NIPD/NIPT. When we arrived at the acronym ‘RAPID’ we had no idea how apt it was going to be, as it is incredible to think how fast things have moved since we first got together to write the outline application in 2007. We now have UKGTN approved tests for fetal sex determination available in several regional genetics laboratories in the UK. Our service at Great Ormond Street is now offering NIPD for a number of single gene disorders (see below) and NIPT for aneuploidy is widely available, albeit currently only in the private sector.

Before going into detail we must thank all of you who have helped with the research, be it recruiting women undergoing invasive tests in your fetal medicine units, answering health professional questionnaires about various aspects of service delivery, or helping us to recruit women and their partners to answer questionnaires which will inform the development of educational packages and appropriate care pathways. We would certainly not be so far along the road towards delivering a comprehensive NIPD service if it were not for the >12,000 samples in the RAPID bank, samples that we and others have used or are using to develop NIPD for a variety of single gene disorders (Table 1) and that we are now using to develop the laboratory and bioinformatic standards to deliver NIPT for aneuploidy in our own regional laboratories. So please keep up the good work. Without your help we will not be able to continue to expand the range of NIPD we can offer for genetic disorders. We would very much like to ask you to focus on collecting samples from families at risk of the conditions listed in Table 1 as these are our priorities at the moment – cystic fibrosis, congenital adrenal hyperplasia, Duchenne and Becker muscular dystrophies and skeletal dysplasias. For CAH and skeletal dysplasias we need maternal blood samples regardless of whether or not parents elected to undergo invasive testing as we can ascertain mutation status from the results of postnatal investigations if necessary.

Briefly, why NIPD or NIPT? Well we tend to use NIPD for those situations which are diagnostic – thus for the diagnosis of Achondroplasia or Thanatophoric dysplasia, we consider that cell free DNA testing is diagnostic and so have stayed with the term NIPD – Non-Invasive Prenatal Diagnosis. For aneuploidy the situation is different, because of the risk of discordant results, confirmation of a positive NIPT – Non-Invasive Prenatal Testing - result via invasive testing is recommended. Maybe we should just use “cell free DNA analysis”, your thoughts on this would be welcomed.

NIPT for single gene disorders

The development of NIPT for single gene disorders is being undertaken by the RAPID team at GOSH and a number of the regional genetics laboratories (Table 1) who are collaborating with RAPID and using samples from the RAPID sample bank. In 2012 gene dossiers for NIPD for achondroplasia and thanatophoric dysplasia (TD) were approved by the UKGTN. At this time the tests were based on a PCFR-Restriction enzyme digest assay that we developed for four FGFR3 mutations, the most common one for achondroplasia, one for TDII and the two most common mutations causing TDF. Whilst this approach was very effective we did have 4/53 inconclusive results in cases at risk of achondroplasia and several cases at risk of TD where we could not detect the less common mutations.
We have since developed a next generation sequencing panel that covers the majority of FGFR3 mutations. This is proving very effective and has proved accurate in all cases tested, including the detection of one rare achondroplasia mutation and several less common TD ones. This panel has just been approved by the UKGTN and we are now beginning to see a shift from invasive to non-invasive testing for these conditions (Table 2). We have offered NIPD to families at risk of other conditions (Table 2) but usually only when we have plasma from an affected pregnancy in the sample bank. This year we will submit gene

dossiers for NGS panels for the exclusion of the paternal CF allele and also for FGFR2 mutations. The main barrier to the development of NIPD for recessive conditions where parents carry the same mutant allele is identifying an accurate way to assess the fetal fraction. However, we are hopeful that taking the NGS panel approach to NIPD will facilitate estimation of fetal fraction. Progress in NIPD for monogenic disorders is slow, but so far as I am aware we are the only country offering definitive diagnostic testing for any single gene disorders. I know of one other European centre focussing mainly on HD,

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Table 1.
Current status of the development of NIPD for single gene disorders in the RAPID programme in the UK

<table>
<thead>
<tr>
<th>Gene / Condition</th>
<th>Laboratory</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR3 NGS panel - achondroplasia, thanatophoric dysplasia etc.</td>
<td>North East Thames Regional Genetics Laboratory, GOSH</td>
<td>UKGTN approved</td>
</tr>
<tr>
<td>FGFR2 panel – Apert etc.</td>
<td>North East Thames Regional Genetics Laboratory, GOSH</td>
<td>Dossier being submitted to UKGTN</td>
</tr>
<tr>
<td>Cystic fibrosis panel</td>
<td>North East Thames Regional Genetics Laboratory, GOSH</td>
<td>Dossier being submitted to UKGTN</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>Haemoglobinopathy Laboratories, Oxford University Hospitals</td>
<td>Under development</td>
</tr>
<tr>
<td>Sickle cell disease and thalassaemia</td>
<td>North East Thames Regional Genetics Laboratory, GOSH</td>
<td>Haemoglobinopathy panel under development</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Department of Medical Genetics, Cambridge</td>
<td>Under development</td>
</tr>
<tr>
<td>Huntington's disease</td>
<td>South East Scotland, Regional Genetics Service, Edinburgh</td>
<td>Under development</td>
</tr>
<tr>
<td>Duchenne and Becker muscular dystrophies</td>
<td>West Midlands Regional Genetics Service, Birmingham</td>
<td>Under development</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>North East Thames Regional Genetics Laboratory, GOSH</td>
<td>IFCAH funding supporting development of NIPD</td>
</tr>
</tbody>
</table>
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“This panel (of FGFR3 mutations) has just been approved by the UKGTN”
The development of NIPT for Down's syndrome, other common aneuploidies and sex chromosome anomalies has continued to move incredibly fast, largely because of the significant commercial drive from the companies desperate to secure a significant part of what is perceived to be a very lucrative market. At the Circulating Nucleic Acids and Proteins meeting in Baltimore earlier this month several speakers spoke of more than half a million tests being done in a total of around 50 countries! However, aneuploidy testing is still only available in the private sector, with significantly more evaluation being required before implementation into public sector routine maternity care – more of that below.

Large scale studies consistently report detection rates of greater than 99% with false positive rates of 0.3-0.5%. The small false positive rate means NIPT for Down's syndrome cannot be considered fully diagnostic and positive results should be confirmed by invasive testing. NIPT for aneuploidy is thus being considered as an advanced screening test and with its increased use we are beginning to see some of the limitations of this test and understand why the problems arise:

- There is an increased rate of failure to report results in women with raised BMI[^3,4] thought to be due to an increased rate of release of maternal cell free DNA (cfDNA) from maternal adipose tissue.
- cfDNA is shed from the placenta, and so it would be reasonable to expect that NIPT might detect confined placental mosaicism (CPM). There are now published reports of CPM being responsible for discordant results[^5], and many more anecdotal reports shared during networking sessions at scientific meetings.
- The sequencing tests used analyse all cfDNA in the maternal blood, this includes cfDNA but the majority emanates from the mother herself. Thus we are testing the mother as well as the baby and so reports of the detection of maternal chromosomal rearrangements are now being published[^6]. Indeed, in one instance a 'discordant' result was found to be due to a maternal malignant tumour secreting an aneuploidy cell line[^7].

We have moved rapidly from diagnosing the major trisomies with NIPT, to routinely determining fetal sex and offering the potential for screening for sex chromosome abnormalities[^8,9] in early pregnancy as at least three companies now offering these options as part of their standard NIPT test. The ease of access of NIPT for anyone who can afford it through the private sector has no precedent in prenatal diagnosis and raises significant ethical concerns. These are concerns that we must address as we consider implementation into routine public sector maternity care. Finally, despite the fact that it is only two years since the clinical introduction of NIPT for aneuploidy[^10,11], we are already seeing publications on the detection of sub-chromosome

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[^3]: [Reference](#)
[^4]: [Reference](#)
[^5]: [Reference](#)
[^6]: [Reference](#)
[^7]: [Reference](#)
[^8]: [Reference](#)
[^9]: [Reference](#)
[^10]: [Reference](#)
[^11]: [Reference](#)
“Introduction (of NIPT) into the public sector requires further evaluation and development of infrastructure”

Evaluation of NIPT for aneuploidy in the NHS

The rapid introduction of NIPT into private medicine has been driven by the commercial sector; whilst we should not procrastinate, introduction into the public sector requires further evaluation and development of the infrastructure required to deliver this test in a safe and appropriate way in routine NHS care. To that end the RAPID team has secured a funded extension to the RAPID programme to evaluate NIPT for aneuploidy in a NHS setting. This study will provide information for the National Screening Committee (NSC) that will be used to inform decisions on introduction of NIPT into the national Down Syndrome Screening (DSS) programme. NIPT will be introduced into the current DSS and diagnosis pathway in five NHS maternity units in London and the South of England, units have been chosen as they represent a variety of approaches to DSS and have a varied ethnic and social mix. We will formally evaluate the changes in uptake of DSS, NIPT and invasive testing, differences in false positive rates between DSS and NIPT, NHS and patient costs, sensitivity of NIPT in a medium-risk population as well as developing health professional and patient educational packages. We have developed a next generation DNA sequencing approach to NIPT in our laboratory at GOSH using an Illumina HiSeq 2500 which was provided by the GOSH Children’s Charity. As part of this project we are developing standard operating procedures and bioinformatics packages that can be rolled out to other Regional Genetics units when the study is completed and they are fully validated. We recruited the first patient to the NIPT arm of the study on 1st November 2013 and plan to end recruitment at the end of December 2014. We are working closely with the NSC and will be meeting them regularly to keep them updated.

How can you help?

• If your service laboratory would like to develop NIPT for a specific single gene disorder not mentioned here, please contact us. If we have samples in the sample bank we would be keen to help you develop further new tests.
• Finally, in order to continue to develop NIPD for a wider range of conditions please do keep recruiting women undergoing invasive tests for any single gene disorder. As we explained above we are particularly keen to have samples from women at risk of carrying a baby with CAH, CF or a skeletal dysplasia regardless of whether or not they have an invasive test.

Further information about RAPID
Email: rapid@ucl.ac.uk
Web: www.rapid.nhs.uk

Acknowledgements
We are grateful to the patients and health professionals who have provided a blood samples or given their time to attend focus groups and/or interviews to allow us to explore stakeholder opinions. Thank you also to all those health professionals who are assisting with sample collection or recruitment to psychosocial studies. This article presents independent research funded by the National Institute for Health Research (NIHR) under the Programme Grants for Applied Research programme RP-PG-0707-10107 (the “RAPID” project). The views expressed here are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

References
NIPSIGEN Study - Translation of Non-Invasive Prenatal Diagnosis (NIPD) for selected Single Gene Disorders into a Clinical Setting.

Stephanie Allen, Julie Hewitt, Samantha Court, Michael Parks, Denise Williams, Trevor Cole, Fiona Macdonald, Mike Griffiths.
West Midlands Regional Genetics Service, Birmingham Women’s NHS Foundation Trust

Since the discovery of cell free fetal DNA in the maternal circulation, non-invasive prenatal diagnosis (NIPD) testing options are increasing to couples. Circulating DNA derived from the placental trophoblast accounts for a small variable proportion of the total free DNA in the maternal circulation. Analysis of this “circulating fetal DNA” in maternal blood is currently becoming a diagnostic possibility for non-invasive diagnosis in many areas of prenatal diagnosis. This is particularly pertinent to those with a pregnancy at risk of a single gene disorder, as with every pregnancy the risk to the fetus may be as high as 50%. For most of these women the only option to determine the fetal genotype necessitates invasive procedures – most commonly chorionic villus sampling from 11 weeks gestation or amniocentesis from 15 weeks gestation, both with the associated risk of miscarriage. Sadly some of the women undergo such procedures repeatedly.

The NIPSIGEN study is a three year project that will focus on the development and implementation into the clinical pathway of new NIPD tests for single gene disorders. This is in collaboration with the NIHR-funded RAPID study, and builds on the repertoire of testing already developed by RAPID. In the first instance the NIPSIGEN study will focus on the development of NIPD testing for Duchenne and Becker muscular dystrophy (DMD/BMD), and will later extend to other disorders such as spinal muscular atrophy (SMA) and congenital adrenal hypoplasia (CAH). For DMD/BMD this is a logical next step in the clinical pathway as non-invasive fetal sex determination is already offered for these pregnancies. In addition, the prevalence of DMD is 1 in 3,500 male births, thus endorsing DMD as one of the more commonly seen genetic conditions that prenatal diagnosis is requested for. Non-invasive fetal sex determination has also been advantageous for women with a baby at risk of CAH, in assisting management of the pregnancy. If the fetus is predicted to be female, early administration of dexamethasone suppresses excessive androgen production which may result in ambiguous genitalia. NIPD would be advantageous to these patients, in allowing further determination of the mutation status of the baby. SMA is also thought to be another good candidate for development of testing. There is a poor prognosis for those affected with SMA as individuals rarely live beyond their second birthday, and leads parents often to request prenatal diagnosis. The estimated incidence of SMA is 7-10 cases per 100,000 live births. A further aim of the NIPSIGEN project is to work on developing a testing protocol for a number of other rare disorders.

To develop and validate testing, plasma samples are required from women with an ‘at-risk’ pregnancy. The project therefore aims to recruit participants from across the United Kingdom that are at risk of having a baby affected with DMD/BMD (group 1). For SMA, CAH other rare disorders and control samples, participants will be recruited through the host site only (groups 2-4). We are able to take advantage of the National Institute of Health Research UK Rare Genetic Disease Research Consortium Agreement (known as the Musketeers’ Memorandum). This agreement enables the Regional Genetics Centres that have signed up to it to participate in a study, allowing the lead site to sign off NHS R&D approval at all sites using a single site-specific information (SSI) form for NHS study approval. This is for rare genetic disease studies which are a non-clinical trial of an investigational medicinal product and do not use any other NHS services. This agreement significantly improves the process that would have previously been required to recruit from all sites. Participants for group 1 will be asked to gift a blood sample when blood is taken for fetal sexing, and a second sample if the fetus is shown to be male. All samples will be anonymised and no results will be available.

The host site, Birmingham Women’s NHS Foundation Trust commenced recruitment of participants in October 2013, and we are awaiting confirmation via the Musketeers’ Memorandum of other sites who would like to participate. Work is also underway in the laboratory to optimise testing protocols. The project will utilise droplet digital PCR (Raindrop and Bio-Rad QX100) and next generation sequencing (Illumina MiSeq) technologies to look at relative mutation dosage (RMD) and relative haplotype dosage (RHDO). The study will run until June 2016 when we hope to have validated assays for DMD/BMD, SMA, CAH, and mutation specific assays for ‘personalised’ mutation testing. The RAPID study has been collecting samples from pregnant women at risk of having a baby with a single gene disorder and appropriate samples from this study will be transferred to the NIPSIGEN study.
The Deciphering Developmental Disorders (DDD) project – which is a collaborative study funded by the Health Innovation Challenge Fund between the Wellcome Trust Sanger Institute and all 24 Regional Genetics Services in the UK and Eire – is now approaching its final year of recruitment. At the date of writing, over 95% of consultant clinical geneticists have recruited patients to the DDD study and collectively we have recruited over 7,000 children with severe undiagnosed developmental disorders, and their parents.

We have recently taken the decision to wind down the array-CGH and will be re-allocating the remaining funding towards exome sequencing. This is primarily driven by the larger diagnostic yield of exome sequencing, and the development of an algorithm to allow us to call CNVs from exome data. We plan to sequence every proband in DDD but will focus our initial efforts on sequencing complete family trios (proband and both parents) primarily due to the large burden of de novo mutations in these children. We are also undertaking a whole genome sequencing pilot using saliva samples from a few families.

We have now reported back over 300 likely diagnoses to clinical teams and families, including 130 de novo point mutations and small insertion/deletion events identified using family exome sequencing and subsequently confirmed in-house using Sanger sequencing. Results from the first ~1100 families are now being written up for publication, and include at least ten new developmental genes with recurrent mutations in phenotypically similar children, which will take our diagnostic yield to around 25%. In addition, uniparental disomy has been identified in six patients in this first cohort using a novel analytical method developed within DDD, and this manuscript is currently under review.

The ethics study that runs within the DDD project has also had a very successful year. Recruitment into the online survey has now finished and we now have data from almost 7,000 people across 91 different countries. Attitudes have been collected on dealing with ‘incidental findings’ within a research setting from members of the public, genetic health professionals, genomic researchers and other health professionals. Results are now being written up for publication, and include both support for data sharing and caution over requiring researchers to actively search for findings outside the scope of their research. Over the next year, the qualitative, interview arm of the study will be developed and views demonstrated in the survey will be explored in more detail face-to-face.

Regular project updates and annual family newsletters can be found on our website, www.ddduk.org.

The project is funded for three years by the Health Innovation Challenge Fund (HICF). HICF is the result of a partnership between the Wellcome Trust and the Department of Health, and aims “to create innovative healthcare products, technologies and interventions and to facilitate their development for the benefit of patients in the NHS and beyond”. The NIPSI GEN study is a portfolio adopted study.

For further information if you would like to participate in the study please contact:

Stephanie Allen, (PI) laboratory: stephanie.allen@bwhct.nhs.uk

Julie Hewitt, Genetic Counsellor (queries regarding recruitment): Julie.hewitt@covwarkpt.nhs.uk

References


Links
• Health Innovation Challenge Fund: http://www.wellcome.ac.uk/Funding/Technology-transfer/Fundedprojects/Health-Innovation-Challenge-Fund/index.htm

• Musketeers’ Memorandum: http://www.bsgm.org.uk/genesics-healthcare-research/nihr-uk-rare-genetic-disease-research-consortium-agreement/

• RAPID study: http://www.rapid.nhs.uk/
“Results from the first ~1100 families include at least ten new developmental genes with recurrent mutations in phenotypically similar children”
The Newsletter of The British Society for Genetic Medicine
Issue 50 February 2014

BSGM News

To all BSGM members

Dear colleagues,

It is with great sorrow that we had to announce the dissolution of the Society for Genomic Policy and Population Health (SGPPH). SGPPH was formed in 2006 and became affiliated to BSGM in 2009. We were successful in establishing membership from a wide range of backgrounds and affiliations, which enriched the society but our numbers have shrank since our affiliation to BSGM. We strongly suspect that it was due to the high membership fees. Nevertheless, we were successful in carrying out council meetings, annual AGM, annual spring conference and a symposium at every BSGM annual conference and we once organised the open debate.

Unfortunately, due to lack of members who can dedicate their time to continue to organise these activities, the burden fell on few of us who extended our membership tenure and worked hard to keep it going, but that became unsustainable. We also learned that the PHG foundation is creating a similar set up, which meant duplicating what we are trying to achieve or worse dividing the affiliation of the total interest group into two camps, when the total number is small to start with. After consulting our membership and having had many discussions with colleagues at SGPPH council meetings, especially the last one on 13 September and discussions with many other BSGM members we reached the inevitable conclusion. Sadly, SGPPH cannot continue as a formal society with AGM, council meetings, a constitution and annual conferences.

Detailed helpful discussions also occurred at BSGM council meeting on 16 September 2013 and our decision to dissolve the Society was accepted. BSGM Officers stressed that BSGM will have to have its own group, even though PHG Foundation is planning to have what they called a ‘PHG Exchange’.

SGPPH has accumulated around £7000 in funds and SGPPH council have decided to allocate the SGPPH funds to the BSGM to hold it in trust and with a restricted access. This fund should be utilised for activities that include meetings, conferences and lectures or similar activities that deal with the population aspects of genomic advances and their impact on public health. Three members of SGPPH council would act as an ‘Advisory Group’ to be consulted and to agree to any spending proposed by either BSGM council or from ex- SGPPH members. Ex-SGPPH members could also convene meetings or seminars to debate in particular public health genomics issues that might arise in the future and they could request this fund accordingly. Professor Sir John Burn also relayed this dissolution message to BSGM members present at the AGM that afternoon.

Finally, it has been my privilege and a rich experience for me being the SGPPH President since 2008. I have worked with many colleagues on the council and in the wider membership who have been very helpful to me and worked hard for the Society. So it may not be the final goodbye but perhaps until we meet again, or until I talk to you again or discuss things with you again on BSGM web pages if we can get the debating forum started!

I am sure many SGPPH members may still like to operate as an informal group with interests around the population aspects of genomics and genetics and the policy implications of these genomic advances. We envisage that this informal group with a possible name of ‘Genomics and Health Forum’ will one day have a discussion group on the BSGM website where we can discuss, debate, encourage meetings, educational and policy issues without the need to have a constitution, council and AGM.

We would also like to offer our expertise in public health genomics to BSGM Council. Although SGPPH will be formally dissolved, our group will continue with our interests and our links and will be happy to contribute to the BSGM Council discussions as co-opted members or in another informal capacity.

The Dissolution of SGPPH
A letter from Dr. Layla Jader
President of the Society for Genomic Policy and Population Health
PHG Exchange: sharing knowledge and views on policy, health and genomics

Philippa Brice
Head of Knowledge and Communications, PHG Foundation

Genomic medicine is here to stay. Whilst we are still a very long way from realising the full potential of genomics to inform and improve prediction, prevention and treatment of disease, the process has undoubtedly begun. Pioneering research and expertise from the traditional BSGM strongholds of clinical, molecular and cancer genetics is helping drive the uptake of genomics into everyday practice in increasing numbers of mainstream specialties. Initiatives such as Genomics England and the 100,000 Genomes Project are further raising the public profile of genomic medicine and provoking debate.

The recent dissolution of the SGPPH as a formal Special Interest Group of the BSGM may reflect the rapidly changing reach of genomic medicine; it is certainly by no means an indication of declining interest and activity at the intersection of genomics, policy and population health. Rather, the number of people with shared interests in issues related to the application of genomics in healthcare and public health (including the many ethical, legal, social and indeed economic considerations these raise) is undoubtedly expanding.

The PHG Foundation naturally shares this enthusiasm, and is keen to build on the SGPPH legacy of multidisciplinary discussion and high quality debate of emerging issues. We are therefore opening our doors to professionals from all sectors with interests in policy, population health and genomics by hosting a new network. The PHG Exchange, which launches in 2014, will provide exciting opportunities for sharing knowledge, ideas and opinions, as well as possibilities for engagement with the policy-making process.

Over the past 15 years the PHG Foundation has been privileged to have the support of experts including many BSGM stalwarts, who have provided a crucial and highly valued element of our own mission to make science (and especially genomics) work for health. In response to the growing range of professional voices with additional perspectives and opinions that should be heard in the policy-making process, we hope that the PHG Exchange will provide a forum for all like-minded individuals, not only geneticists and associated health professionals and a broad range of researchers, but also policy-makers, clinicians and public health professionals, commissioners, legal and regulatory experts, commentators and advocates.

For a modest membership charge (to partially offset running costs), members will be able to join cutting-edge meetings and discussions on issues of mutual interest; network with other professionals; and enjoy a range of associated benefits, including priority communications and knowledge products from the PHG Foundation. We can promise that speakers will never be dull, and with guidance from both members and an external Advisory Board, topics should always be relevant. Participation will definitely be rewarded, and a particularly warm welcome extended to all BSGM members!

BSGM has recognised the changing (and in many respects highly favourable) environment for genetic medicine and responded with forward-looking adaptations – new name, website, conference venue - whilst maintaining its core activities and repute. We want to move with the time too; PHG Exchange is our provision for all those who share interests in genomics, policy and population health to enjoy ongoing, informal exchange of expertise and ideas.

For more information about the PHG Exchange, see our website at: www.phgfoundation.org/phgexchange
NIHR Collaborative Group for Genetics in Healthcare – update

James Brooks, Science Editor, Progress Educational Trust
Siobhan Chan, Genetics Editor, Progress Educational Trust
On behalf of the NIHR Collaborative Group for Genetics in Healthcare

1. Practical Research in Genetic Healthcare Session: BSGM Liverpool 2013

NIHR Clinical Research Network (CRN) supported researchers shared their success stories and outlined plans for future studies at the British Society of Genetic Medicine’s annual conference held in Liverpool in September 2013.

Professor Sir John Burn, professor of Clinical Genetics at Newcastle University, started off the session by giving an update on the next clinical research study in the Cancer Prevention Programme study, CaPP3.

Previous CaPP studies have shown that aspirin can reduce the risk of cancer in those with Lynch syndrome, an inherited predisposition to cancers of the colon and rectum. Of the 861 patients tested, 10 percent of those not taking aspirin developed colorectal cancer, compared to six percent of those who had taken 600mg of aspirin every day.

The next stage of the study will determine the level of aspirin that is needed to prevent cancer without causing adverse side effects such as stomach ulcers or cerebral haemorrhage. Researchers will compare the effects of 100mg, 300mg and 600mg doses when taken every day for two years.

“We are testing the effects of a baby aspirin, one standard aspirin and two aspirins,” said Sir John. “Two aspirins a day is regarded as a high dose, so if lower doses are still able to prevent cancer, then we can avoid side effects.”

The study will look at 3000 people with Lynch syndrome worldwide, with recruitment in the UK being driven through the Regional Genetics services and the NIHR Genetics Specialty Group.

Professor Julian Sampson, head of Medical Genetics at Cardiff University, also outlined his current UKCRN portfolio study, TRON (UKCRN 13640) which will test the effectiveness of the drug everolimus in people with tuberous sclerosis.

Tuberous sclerosis is a rare genetic disease where non-cancerous tumours grow on organs such as the brain, heart and kidneys. It is also associated with memory and behavioural problems and is linked to autism.

“The drug everolimus puts a brake on the faulty cellular signalling pathway,” says Professor Sampson. “There have been many clinical trials showing that it shrinks kidney tumours and brain growths in those with tuberous sclerosis. Our study aims to show that everolimus can improve memory and ‘executive functions’ such as attention, problem-solving and planning.”

However, given the rarity of the disease, the trial has seen difficulties recruiting patients. But with the help of UKCRN supported research nurses, Professor Sampson hopes that suitable patients can be identified across the UK.

Delegates were then given an insight into the commercial consideration for supporting such trials like TRON during the presentation by Dr Matthew Hickling, Therapeutic Area Medical Head at Novartis Pharmaceuticals UK. Dr Hickling reminded the audience why research into medicines for rare genetic diseases is important, citing that approximately 3.5 million people in the UK will be affected by a rare disease at some point in their lives, 75 percent of these being children.

Dr Hickling then offered some advice to those seeking to collaborate with the pharmaceutical industry, advising them to “be mindful of the commercial perspective”. Companies develop ‘target product profiles’ for products providing a list of potential areas of interest to explore further with clinicians. Other commercial considerations for developing products beyond demonstrating efficacy is ensuring access and reimbursement; this can prove more challenging when meeting the unmet need of rare diseases.

Current drug development may take an average of 10 years from concept to market authorisations; the cost of which may be in excess of one billion Euros. “This is no small undertaking in terms of cost and time,” said Dr Hickling. “You need to be certain that the next study, which may cost a couple of million pounds, is really going to derive a benefit for patients and treating physicians as well as ultimately see some form of return on investment or scientific value for the company.”

In developing investigator initiated studies like TRON, “Engage early, and have a clear idea of what you want to undertake,” advises Dr Hickling. Important considerations are study timelines including recruitment, intellectual property rights, drug supply as well as publication planning in advance of securing funding. Dr Hickling also highlighted the importance of understanding the patient population: knowing how to identify patients in the clinical community and making sure they will have access to any resulting treatments.

Engaging with patients and support groups was also brought to light in the talk by Professor Andrew Wilkie, Nuffield Professor of Pathology at Oxford University.
The Newsletter of
The British Society for Genetic Medicine
Issue 50 February 2014

BSGM News

Professor Metcalfe also described how families may not feel they have sufficient information and support from healthcare professionals. "Many genetic counsellors certainly advise them to talk to their children, but they don’t tell them how to engage in any conversations or how to initiate any discussion," she said. This can make it difficult to approach the subject, but Professor Metcalfe hopes that her team’s multi-disciplinary approach will help families to be able to better communicate. Working with genetic counsellors, nurses, families and support groups, they are aiming to develop interventions that could support families much more effectively, including multi-family discussion therapy and developing narratives that could be used as a springboard for questions (UKCRN 14128: Talking to Children about Inherited Genetic Conditions).

Whether through refining genetic counselling, reducing the risk of side effects from medication, or ensuring access to interventions, the session highlighted the importance of putting the patient first: an essential approach in genetic research.

2. Consent and Confidentiality in Genetic Medicine

As genetic testing expands so does the realisation; genetic test results can unleash a raft of ethical dilemmas for patients and practitioners alike. Should a risk gene carrier inform the rest of their family that they, too, might be carrying the mutation? If so, who, exactly, should be told? If not, do medical professionals have a duty to act? What about patient confidentiality?

Many ethicists have contributed answers to these questions. But more empirical research into how both patients and healthcare professionals view these dilemmas is thin on the ground.

The new UK Clinical Research Network (UKCRN 13870) portfolio study ‘Consent and Confidentiality in Genetic Medicine’ aims to rectify that.

Professor Wilkie described genetic discoveries in craniosynostosis (UKCRN 7424: Genetic basis of craniofacial malformations), a condition where the bones in the skull become fused together, which can lead to a build up of pressure in the skull.

His team has been able to identify two new genetic mutations, which has allowed the development of diagnostic clinical tests. This significant advancement has had a huge impact on families and patient support groups, Professor Wilkie described. He read out a letter from Headlines, a craniofacial support group magazine. "When Charlie was finally diagnosed, it came as a relief that somebody had listened to us and was able to put a name to the problem," wrote a parent whose child had finally been diagnosed with a genetic mutation.

"This is what motivates us all – to get feedback from families," said Professor Wilkie.

Professor Alison Metcalfe from King’s College London also described her experience with families with genetic conditions.

“One of the things I’ve found is that many families struggle to talk about (the) genetic condition affecting their family – particularly parents talking to their children," she said.

Professor Metcalfe cited a number of barriers to open discussion within a family, such as the emotional anxiety involved, being physically tired after caring for a family member affected by the condition, and worrying that a serious discussion would impact on fun quality time together.

From left to right: Dr Shane McKee (Chair), Professor Sir John Burn, Professor Andrew Wilkie, Professor Alison Metcalfe, Mr Alastair Kent (Chair), Dr Matthew Hickling, Professor Julian Sampson
Dr Sandi Dheensa, a senior research fellow in clinical ethics and law at Southampton University is managing the project together with principal investigator Professor Anneke Lucassen and Dr Angela Fenwick.

Dr Dheensa has already begun the one-on-one patient interviews and focus groups with medical professionals that will form the backbone of the project. Despite this emphasis on empirical research, one of the central questions the study will investigate is, Dr Dheensa says, “quite an abstract one. And that is: what is the nature of genetic information? And from that, does a person own their genetic information or does it belong to a family?”

There are many ramifications to the answer here, Dr Dheensa continues. Importantly, if genetic information is not the patient’s property then do they need to consent for it to be passed on to, or accessed by, family members?

More immediately, Dr Dheensa’s first interviews have alerted her to clinical scientists’ concerns as to whether patients undergoing genetic tests are being adequately informed of the potential implications for the rest of their family and whether they have given sufficient consent.

Accordingly, a priority for the study now is to interview specialists outside genetic medicine – the doctors who are commissioning the tests - to see if they have similar concerns.

"Before genetics becomes incorporated fully into mainstream medicine it’s important to understand how genetic testing is being presented to people, outside of the genetic service", Dr Dheensa explains.

Ultimately, the study will be used to inform updated guidelines for clinical genetic practice. The team also plans to develop literature aimed at helping patients, family members and healthcare professionals make decisions about testing. These leaflets or booklets will touch on issues like risk and consent; issues that will be very familiar to clinical genetics professionals but maybe less so to those outside.

Although the study – and participant recruitment – is in its early stages, Dr Dheensa says that the involvement with the UK CRN and the NIHR Genetics Specialty Group has already been helpful. “Our study will involve quite a diverse group of participants. Thanks to the interest from the UK CRN and the NIHR Genetics Specialty Group I feel like I’m not just on my own trying to find these people - there’s actually a network of people who can help me with it.”

3. The EMBRACE Study – an update

A study into familial breast cancer is embarking on its next phase in an effort to prevent cancer in high-risk women.

The EMBRACE study (UKCRN 1358) – Epidemiological Study of Familial Breast Cancer - looks at women with BRCA1 or BRCA2 genetic variants, who are at higher risk or breast or ovarian cancer or have already been affected by them.

The team previously looked at women who had breast cancer and retrospectively identified a number of risk factors that increased the chances of the condition. This includes the number of children they have had, their age at menarche (onset of periods), and exposure to radiation, for example if they had chest X-rays taken at a young age.

The next stage of the project will be a prospective analysis: assessing risk factors in women with the BRCA genes who do not have cancer, and finding out how best to manage women at high risk.

"The project will help us to identify the women who are at highest risk of developing breast or ovarian cancer, how to reduce the chances of this happening, and how best to treat those who have been affected," said Douglas Easton, Professor of Genetic Epidemiology at the University of Cambridge.

The team are joining forces with large genetics studies worldwide as part of the International BRCA1/2 Carrier Cohort Study (IBCCS) so that they can analyse data on a larger number of people. Information from several centres around the world, including the Netherlands and France, will be combined. "In total, around 30,000 participants will be taking part in this project," said Professor Easton. "We hope this will allow us to get more accurate results."

The work will also assess how the level of risk changes over time, which will allow clinicians to advise women on when medical interventions would be most useful.

The team are already beginning to piece together the data on how to prevent cancer in those with a BRCA mutation. They have found that prophylactic surgery is the most effective means of preventing breast or ovarian cancer. Oophorectomy, removal of the ovaries, was seen to reduce the risk of ovarian cancer by 80 percent as well as reducing the risk of breast cancer by an estimated 50 percent, thought to be the result of lower levels of oestrogen being produced.
“Genetics is currently the top performing NIHR Specialty Group”

Dr Gill Borthwick, National Research Coordinator for the CGGH, opened the day with good news all round. Genetics is currently the top performing NIHR Specialty Group as judged by a number of the NIHR key recruitment metrics.

There was also news of the advance of the NIHR UK Rare Genetic Disease Research Consortium Agreement, which has also come to be known as the ‘Musketeers’ Memorandum’. This initiative was instigated to cut through some of the red tape that is particularly prohibitive to clinical genetics research on rare diseases.

The Memorandum, which 18 UK NHS Organisations that host Regional Genetic Services have now signed up to, was necessary because in many cases “more administrative staff were involved in the permission process than there were patients with the disease”, Dr Borthwick said.

A talk on ethics by a professor at the University of Oxford may have set some fearing 40 minutes of airy philosophising, but the presentation by Professor Michael Parker, Director of the Ethox Centre, was no less grounded in everyday genetics research than Professor Rahman’s.

Much of the discussion led by Professor Parker focused on consent and its importance in genetic research. After a quick look at how ethicists classify responses to research dilemmas, attendees were given a case study to consider. Although the study in question looked relatively straightforward - and was entirely plausible - it threw up a wealth of ethical questions.

Two group sessions followed lunch. In the first, representatives from genetics portfolio studies presented news of how they were getting on and Lauren Roberts gave an update on SWAN UK activities. Then came a group discussion on ‘Recipes for Recruitment’. This session was concluded by Professor Sir John Burn, leader of the CGGH in somewhat geographically partisan fashion.

Success in study recruitment, said Sir John, could hardly be accused of a lack of ‘Theatre’ during the final talk of the day focusing on the CaPP3 study which he is
5. Tuberous sclerosis trial needs recruits; can you help?
A randomised, double blind, placebo-controlled study of Everolimus in the treatment of neurocognitive problems in tuberous sclerosis, opened to recruitment in 2012. The UK Clinical Research Network portfolio study (UKCRN 13640) is an investigator led study supported by Novartis Pharmaceuticals and the Tuberous Sclerosis Association. Due to the rare nature of the condition Professor Julian Sampson, who is leading the study needs to identify recruits from across the UK.

Tuberous sclerosis is a rare genetic disease where non-cancerous tumours grow in organs such as the brain, heart and kidneys. It is also associated with learning and behavioural problems and is linked to autism.

"There have been many clinical trials showing that the drug everolimus shrinks kidney tumours and brain growths in those with tuberous sclerosis," says Professor Julian Sampson, Head of Medical Genetics at Cardiff University, who is leading the research.

"Our study will show whether everolimus can improve memory, attention, problem-solving and planning in people with tuberous sclerosis who have difficulties in these areas."

Tuberous sclerosis is caused by mutations in the TSC1 or TSC2 gene. Around one-third of patients inherit the condition from a parent, and two-thirds of cases are caused by de novo mutations. The mutations cause the mTOR cell signalling pathway to become over active, a process that everolimus can 'put a brake on'.
As well as receiving credit for helping us to recruit patients, nurses at regional genetics centres will be able to see their patients with rare genetic diseases being enrolled onto clinical trials that could benefit their health."

Professor Sampson also recommends engaging with patient support groups early on in the research process. The Tuberous Sclerosis Association has provided funds to reimburse all travel and accommodation costs for families involved in the study.

http://medicine.cf.ac.uk/tron-study/tron@cardiff.ac.uk

Further information on portfolio studies can be found on the UK Clinical Research Network (UKCRN) Portfolio Database
http://public.ukcrn.org.uk/search/

If you think your research could benefit from the NIHR Genetics Specialty Group’s services visit http://www.cmcc.nihr.ac.uk/about_us/ukcrn/specialty/genetics or email Dr Gill Borthwick, the Genetics National Research Coordinator, on Gillian.borthwick@ncl.ac.uk.

These articles were prepared by the Progress Educational Trust on behalf of the Collaborative Group for Genetics in Healthcare (CGGH), working with the NIHR Genetics Specialty Group.

As Genomics England rolls out its 100,000 Genomes Project, a flagship project from the PHG Foundation aims to facilitate the ethical, legal and socially responsible introduction of genomic testing, for the benefit of patients and clinicians. Realising Genomics in Clinical Practice is based around a series of four invited stakeholder workshops taking place in 2013–2014. Led by PHG’s ethical and legal expert, Alison Hall, the work is a progression from the Foundation’s 2011 report *Next steps in the sequence* - the first comprehensive report into the implications of whole genome sequencing for health in the UK.

One of the main ethical challenges raised in that report is the potential for incidental findings to be generated from whole genome sequencing (WGS) requiring policy approaches to be developed to minimise negative consequences. In *Realising Genomics* we focus on the ethical, legal and social challenges of implementing whole exome sequencing (WES) and whole genome sequencing and in particular, the ways in which these should be addressed when implementing these technologies into clinical practice.

**ELSI and the implementation of WGS/WES in clinical practice**

At the first workshop, held in July at Madingley Hall, Cambridge, the PHG Foundation assembled an international group of researchers from the fields of ethics, law, social sciences, biosciences, medicine and public health. Over two days, they explored the findings from their preliminary research and contributed insights to address the thorny ethical issues likely to arise as the implementation of WGS/WES into clinical practice advances.

Whilst the variety of expertise generated a range of perspectives, some distinct
themes emerged, not least the lack of consensus about the meaning and usage of terms such as ‘unexpected’, ‘unsolicited’ and ‘incidental’ findings – i.e. findings that fall outside the primary purpose of testing. Notably, it became clear that although clinicians state that patients should be warned about the generation of these findings, in practice a consistent approach within the consent process has not yet been established.

**What is the relationship between research and the clinic?**
The group agreed that two ethical principles are paramount in both research and clinical settings: respect for autonomy and beneficence. However in each setting, the duties, responsibilities and expectations of stakeholders - including clinicians, patients, researchers and regulators - may result in different ethical priorities.

A discussion of relevant ethical, legal and social issues identified the need for new approaches to gaining informed consent, clear guidelines for the handling of unexpected results, and the changing nature of the research-clinical interface. As the boundaries between research and the clinic blur, it may be time to consider a new paradigm, perhaps incorporating elements of the ethical principles underpinning both activities. The relationship between research and the clinic in genomics, and the nature of a possible hybrid model was the focus of the second workshop in December 2013.

The main ethical, legal and social challenges raised by the implementation of WGS technologies into clinical care were debated and prioritised into seven themes (see Image).

**Patient pathways and policy directions**
Work in 2014 will continue with an exploration of current patient pathways and how they may need to adapt in order to achieve better care for patients through the use of genomic technologies that is both affordable and equitable. The final workshop, scheduled for the summer, will bring together the findings of the preceding workshops, along with additional research, to formulate policy recommendations and guidelines.

Updates from *Realising Genomics in Clinical Practice*, including interim findings from the workshops, will be available from the PHG Foundation website: www.phgfoundation.org
Genetics trainees step into action for STP

Jennie Bell, Professional Lead, Cellular Sciences and Genetics, National School of Healthcare Science.

In September 2013 the National School of Healthcare Science (the School) welcomed a new cohort of future leaders in healthcare science.

Eighteen genetics trainees joined over 200 of their fellow colleagues embarking on the NHS Scientist Training Programme (STP) across 28 specialisms.

Among them were 13 trainees in clinical bioinformatics the first intake of its kind under the Modernising Scientific Careers programme.

The STP has grown to over 700 trainees, having started with just 16 trainees on the genetics pilot programme in 2009. It is pleasing to see that those 16 trainees who started that journey four years ago successfully completed the programme and are now making a significant contribution to delivering quality patient care in the health service.

Applications for STP posts to start in September 2014 will open in January. Applicants are encouraged to visit www.nhschoices.nhs.uk/stp for the latest information on how to apply.

The training programmes continue to have a positive impact in the delivery of healthcare as highlighted by the Guardian Healthcare Innovation Awards 2013, who named Modernising Scientific Careers winner of the Workforce Innovation Award.

The news was announced at a ceremony held in London on 24th October. The judges praised the programme for "The magnificent way they showed leadership in taking people with them in developing the programme. They involved patients and staff in developing it and brought with them the professions and the academic institutions. A great win!"

The Chief Scientific Officer, Professor Sue Hill, sees the award as a tribute to the many healthcare science professionals, patients, academics and others who have contributed to the development of the Modernising Scientific Careers programme. Further information about the award can be found at http://www.theguardian.com/healthcare-network/2013/oct/25/winner-workforce-innovation

It is important to particularly recognise the significant contribution genetics has made to the success of this training programme through the pilot work. This has included the development of:

- an assessment strategy across the whole programme that provides both internal and external review of the trainee’s development
- a quality assurance strategy for departments delivering the training in the work place
- integrating cytogenetic and molecular genetic training of clinical scientists
- a rotational year that takes trainees into other specialist areas of scientific healthcare
- an online assessment portfolio that is accessible to trainees, trainers and the School
- training of trainers to equip them for the delivery of the training programme.

All of this is managed and supported by the School based within Health Education England (www.hee.nhs.uk) in the West Midlands.

Much work remains to be done to continue to support the development of these programmes, in particular the clinical bioinformatics programme and the Higher Specialist Scientific Training Programme (HSST).

The School works closely with the Workforce Development Committee of the Association of Clinical Genetic Scientists chaired by David Baty and the School’s Professional Lead for Cellular Science and Genetics, Jennie Bell and numerous members of the profession in many different capacities.

Genetics has benefitted from the opportunity to contribute to the development of the STP but only through the hard work and commitment of the trainees and training departments; we should be proud of all that has been achieved so far.

Visit www.nshcs.org.uk for information about the National School of Healthcare Science.
Update from NGRL Manchester – highlights from the last 6 months

Andrew Devereau

**DMuDB**

Current development work is focused on linking DMuDB with popular laboratory systems and software. We have collaborated with Interactive Biosoftware to integrate a DMuDB variant track into their Alamut browser interface – this will enable anyone with a DMuDB account to display DMuDB data in their Alamut view. We also continue our work with STARLIMS to produce an ‘Export to DMuDB’ module to enable STARLIMS implementers to build data submission into their workflows.

We have also embarked on two related projects that will expand and advance the scope of our database capabilities. A pilot project is underway to assess the use of PhenoTips, an open source tool that facilitates the collection of phenotypic data in a standardised electronic format. This is essential if phenotypic data are to be available for computational analysis – for example as part of bioinformatic analysis pipelines for next generation sequencing data. In a second project we are developing a new database specifically for the collection and sharing of NGS data and investigating how to integrate this resource with the bioinformatic pipelines that NGS teams use to analyse new sequence data.

**SNPCheck**

Recent developments have seen the inclusion of Minor Allele Frequency scores in the Excel export of results; the addition of edit, copy and paste controls to make management of saved primer sequences easier; and an update to the latest build of dbSNP.

**Training**

In August we welcomed Jan Taylor who has joined NGRL Manchester and Nowgen in the role of Clinical Bioinformatician and Trainer. Jan is leading the delivery of the NGRL/Nowgen bioinformatics training programme and the development of bioinformatic projects for NGRL Manchester.

NGRL, with University of Manchester and The Nowgen Centre, has been awarded the contract to deliver the first NHS Scientist Training Programme in Clinical Bioinformatics as part of the Modernising Scientific Careers programme. The first teaching module has been completed, with positive feedback from the students.

In August NGRL and Nowgen provided a bespoke on-site two-day course in bioinformatics for clinical genetics to the Dublin clinical genetics centre. Further enquiries about the delivery of on-site courses should be emailed to training@nowgen.org.uk.

**Grant funded projects**

**EuroGentest** – NGRL has produced guidelines for the collection, representation and sharing of clinical genetic data (developed during a workshop held in January 2013 on the same subject). A training workshop focused on the tools, resources and concepts covered in the guidelines was delivered in December 2013. Outputs from this project are available on the NGRL website: www.ngrl.org.uk/Manchester/page/eurogentest.

A New Career Path within Genomic Medicine

Angela Davies, Professional Training Manager, Nowgen

A Manchester team has helped the Department of Health address a bioinformatics skills shortage in genomic medicine that will assist the diagnosis and management of genetic conditions. Dr Angela Davies from Nowgen, Professor Andy Brass from the School of Computer Science at The University of Manchester and Andrew Devereau from the Manchester National Genetics Reference Laboratory (NGRL) have developed the MSc course in clinical bioinformatics, now being delivered by the team at Central Manchester Hospitals/The University of Manchester. The MSc is part of the new Clinical Bioinformatics (Genetics) Scientist Training in the Modernising Scientific Careers Programme that assists trainees from the NHS to develop the knowledge and skills to analyse and interpret genomic data; this is one of several programmes coordinated by Manchester Academy for Healthcare Scientist Education (MAHSE). This course focuses on problem-based learning, including the analysis and interpretation of data from anonymised clinical genetics cases. The first cohort of 14 students started at Manchester in October 2013.

For further information contact: angela.davies@manchester.ac.uk

Professor Andy Brass working with a group of students
Service developments

Cardiomyopathy Testing: Oxford Announce Three New Multi-Gene Panels

Jesse BG Hayesmoore, Oxford

The Oxford Medical Genetics Laboratory has provided molecular genetic testing for cardiomyopathies for ~10 years. During this time, it has seen its portfolio of services grow from screening of single genes in 2003, to a four gene screen in 2006, through to its highly successful 13 gene hypertrophic cardiomyopathy screen. This latter service, launched in 2011, was one of the first clinical molecular genetic services in the UK to utilise massively parallel sequencing technology. Now, in 2013, the lab is excited to announce the launch of three new, more comprehensive, cardiomyopathy services.

Cardiomyopathies are a heterogeneous group of diseases that affect the structure and function of myocardium (heart muscle), and are an important cause of sudden death. They are commonly inherited, usually in an autosomal dominant manner with incomplete penetrance and variable expressivity. The most common, affecting ~1 in 500 adults, is hypertrophic cardiomyopathy (HCM), which is characterised by abnormal thickening of the myocardium, particularly of the left ventricle. The other main types are dilated cardiomyopathy (DCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC). DCM is defined by the presence of a dilated and poorly functioning left ventricle. The hallmark of ARVC is replacement of myocardium with fatty tissue and fibrosis. Clinical differentiation of these conditions can be difficult, as there is considerable phenotypic overlap.

Similar to the Joubert syndrome and inherited ataxia services announced last year (issue 49, page 35), the new services for HCM, DCM, and ARVC, utilise Agilent’s HaloPlex Target Enrichment System combined with Illumina’s MiSeq Personal Sequencer. Whilst the new HCM and ARVC panels should slightly increase clinical sensitivities (relative to previous offerings), the complete 28 gene panel (see Table 1) represents a much greater service improvement for DCM. Designed in collaboration with Professor of Cardiovascular Medicine, Hugh Watkins, and with careful consideration of recent scientific developments, this panel represents the first in the UK to provide a comprehensive multi-gene test targeted specifically at idiopathic DCM. With an estimated clinical sensitivity of 30–40%, the range of genes includes all 16 that make up the HCM panel, all eight in the ARVC panel, and four DCM-specific genes. Although mutations in many of the HCM genes (especially those that encode sarcomere proteins) are known to also cause DCM, the remainder are also included to account for the phenomenon of ‘burnt-out HCM’, an end-stage DCM-like phenotype that affects up to 10% of HCM patients. Similarly, the eight ARVC genes are included due to the phenotypic overlap between DCM and ARVC.

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Price (UK NHS): £POA* £1,020 £1,020*

*The price of the ARVC panel includes MLPA dosage analysis of PKP2.
*Please contact the laboratory for the current price of the HCM panel.
Of the 28 genes, two deserve special mention. The first is *LMNA*, which encodes the nuclear envelope protein lamin A/C. In addition to DCM, mutations in this gene are known to cause a wide range of disorders including Emery–Dreifuss and limb-girdle muscular dystrophies, familial partial lipodystrophy, Charcot–Marie–Tooth disease, and Hutchinson–Gilford progeria syndrome. They are detectable in up to 6% of DCM patients or in up to 33% of DCM patients with conduction defects, and are associated with a particularly high risk of lethal arrhythmia. Recent evidence also indicates that LMNA mutations can be detected in up to 4% of patients with an unexplained clinical diagnosis of ARVC.

The other notable gene is *TTN*. This gene encodes titin, which, at >33,000 amino acids long, is the largest known human protein. It plays a key role in sarcomere assembly, transmission of contractile force, and maintenance of resting tension. Although originally linked to DCM in 1999, the gene has escaped routine mutation screening efforts due to the technical challenge posed by its large size (>100 kb of coding sequence across >350 exons). That is until last year when Harvard-based Seidman and colleagues published data, which showed that truncating *TTN* mutations account for ~25% of familial and ~18% of sporadic DCM cases, making *TTN* the most frequent known genetic cause of the disorder. This large contribution brings molecular genetic testing for DCM more in line with recent guidelines, which require cardiomyopathy gene panels to either inform a potential change in clinical management or to have a clinical sensitivity of >40%. In the Oxford DCM panel, all exons expressed in the major cardiac *TTN* isoform are screened. Due to a dearth of understanding regarding the effects of missense changes in *TTN*, only truncating mutations are reported.

Referrals for all three services are accepted from clinical geneticists, cardiologists, and other relevant medical specialists (in liaison with clinical genetics). A clear and informative report will be issued within 60–80 days. For further information, please visit the website (http://www.ouh.nhs.uk/geneticslab) or use the contacts below. Feedback from service users will be gratefully received.

**Laboratory Contact:**
Karen McGuire. Tel: 01865 225594. E-mail: Karen.McGuire@ouh.nhs.uk

**Clinical Lead:**
Dr Edward Blair. Tel: 01865 225476. E-mail: Ed.Blair@ouh.nhs.uk

**References**
Service developments cont.

Next generation sequencing in Exeter – new exome and genome service now available

Sian Ellard, Exeter

The Exeter Molecular Genetics Laboratory is an integrated research and diagnostic testing facility which provides testing for >50 genetic disorders, molecular pathology tests and has an international reputation for its research into monogenic diabetes and hyperinsulinism.

Next generation sequencing was initiated in 2010 with the purchase of an Illumina GAII which has subsequently been upgraded to a HiSeq 2500. We have developed a wide range of applications that include targeted, exome and genome sequencing (see below). Nearly 800 patient samples have been tested in house (515 targeted NGS, 238 exomes and 5 genomes) and we are pleased to announce the addition of exome and genome sequencing to our diagnostic test repertoire.

<table>
<thead>
<tr>
<th>Application</th>
<th>Disorder</th>
<th>Reference</th>
<th>Diagnostic service</th>
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<tbody>
<tr>
<td>Targeted NGS (29 genes)</td>
<td>Monogenic diabetes</td>
<td>Ellard et al¹</td>
<td>Yes (£650)</td>
</tr>
<tr>
<td>Gene specific genomic sequencing to detect deep intronic mutations</td>
<td>Hyperinsulinism</td>
<td>Flanagan et al²</td>
<td>Yes (founder mutations included in Sanger test)</td>
</tr>
<tr>
<td>Characterisation of translocation breakpoints by genome sequencing</td>
<td>Split hand foot malformation</td>
<td>Lango-Allen et al J Med Genet In press</td>
<td>Yes (£1500)</td>
</tr>
<tr>
<td>Trio exome sequencing</td>
<td>Syndromic pancreatic agenesis</td>
<td>Lango-Allen et al³</td>
<td>On request</td>
</tr>
<tr>
<td>Case series exome sequencing</td>
<td>MDP syndrome</td>
<td>Weedon et al⁴</td>
<td>N/A</td>
</tr>
<tr>
<td>AD Linkage exome sequencing</td>
<td>Charcot-Marie-Tooth disease</td>
<td>Weedon et al⁴</td>
<td>On request</td>
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<tr>
<td>AR Linkage genome sequencing</td>
<td>Isolated pancreatic agenesis</td>
<td>Weedon et al⁴</td>
<td>N/A</td>
</tr>
<tr>
<td>AR Linkage exome sequencing</td>
<td>Lethal disorders detected by antenatal ultrasound scan</td>
<td>Ellard et al Submitted</td>
<td>Yes (£1500)</td>
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</table>

In bold (see table above) are two applications that may be useful for patients seeking genetic testing via clinical genetics centres. The characterisation of translocation (or inversion) breakpoints by low depth genome sequencing allows resolution of breakpoints at the level of the nucleotide (confirmed by Sanger sequencing) to determine the likely consequence of the rearrangement in relation to the clinical phenotype. In our patient with split hand foot malformation a translocation breakpoint within the 7q22 band was reported by karyotyping but genome sequencing showed that the breakpoint is actually in 7q32 and will separate the recently characterised DYNC1I1 exonic enhancers from their target genes DLX5/6 which are required for normal limb development. This methodology can be applied to any patient with a translocation or inversion where knowledge of the precise breakpoint(s) is potentially informative.

When we discussed possible applications of exome sequencing with our clinical genetics team, one suggestion was the situation where a couple has had multiple pregnancies terminated due to a likely autosomal recessive disorder. DNA samples from these fetuses cannot be
tested within the auspices of the DDD study because the affected individuals were never born. In the south west of England most of these couples are non-consanguineous and the likely scenario is that the fetuses have inherited different heterozygous mutations from each parent. We developed a strategy to perform exome sequencing in the parents and then test for co-segregation of rare potentially deleterious heterozygous variants. Exome sequencing is performed on parental samples rather than fetal material because of the limited quantity/quality of DNA available for the latter. In eight couples of European ancestry we found an average of one gene (range 0-4) where both partners were heterozygous for rare potentially deleterious variants. A proof of principle study detected heterozygous DYNC2H1 mutations in a couple who had multiple fetuses with short rib polydactyly. Prospective analysis of two pregnant couples with a history of multiple terminations for fetal akinesia was performed and a diagnosis obtained in one family through the identification of compound heterozygous RYR1 mutations. In view of a normal ultrasound scan at 20 weeks they decided not to risk miscarriage by undergoing invasive testing, but are delighted to have this option for their next pregnancy.

Please contact Professor Sian Ellard (sian.ellard@nhs.net or ring 01392 402910) if you’d like to discuss any potential cases/families.

References

Service developments cont.

Connective Tissue Disorders NGS Service

Mandy Nesbitt and Rebecca Pollitt, Sheffield

The Sheffield Diagnostic Genetics Service are pleased to announce the launch of a range of next generation sequencing (NGS) tests across the Connective Tissue Disorder service within the department.

Connective tissue disorders form a large and heterogeneous group of disorders, and many genes and pathways contribute to the pathogenicity. Some of the more common disorders include osteogenesis imperfecta, various forms of Ehlers Danlos syndrome, familial aneurysm syndromes including Marfan syndrome, and familial porencephaly. Features of these disorders can include joint hypermobility, skin elasticity, easy bruising, bone fragility, bone or limb deformities, blood vessel or organ rupture, small vessel brain disease, scleral abnormalities and ocular rupture. There can be considerable clinical overlap between these conditions.

The Connective Tissue Disorders service has introduced eight panels of genes which complement and extend the existing Sanger sequencing services. Recently described genes associated with autosomal dominant and autosomal recessive osteogenesis imperfecta have been included in the panels to allow comprehensive genetic investigation for this condition. Ehlers Danlos syndrome (EDS) panels have been designed for each of the clinical classification subtypes: vascular, classical and kyphoscoliotic. Investigation for type IV collagen related small vessel disease, including familial porencephaly, is also offered.

The introduction of a single panel for familial thoracic aortic aneurysm disorders, which includes Marfan syndrome, vascular EDS, Loeys-Dietz and other recognised familial aneurysm syndromes, provides comprehensive ‘one stop’ genetic diagnostic analysis for this group of patients.

The NGS panels currently include 37 genes that are known to be associated with connective tissue disorders; however more genes and panels will be added in the future to continue to progress and improve the service offered.

All panels use the SureSelect target enrichment protocol and Illumina’s MiSeq system to perform the next generation sequencing. Full bioinformatics analysis is undertaken and any potentially pathogenic mutations are confirmed using Sanger sequencing prior to reporting.

For more information on the Connective Tissue Disorders service please see our website (http://www.sheffieldchildrens.nhs.uk/our-services/laboratory-medicine) or contact the laboratory (Mandy Nesbitt / Rebecca Pollitt tel: 0114 2717003).
Service developments cont.

Distal Arthrogryposis – Sequence analysis of the $\text{TPM2}$ gene

Julie Honeychurch, Bristol

A new diagnostic service for Distal Arthrogryposis syndrome ($\text{TPM2}$ sequence analysis) is now available at Bristol Genetics Laboratory. A gene dossier for this new service was accepted by UKGTN in July 2013.

Distal Arthrogryposis (DA) is a group of disorders characterised by congenital contractures in the distal limbs without an obvious neurogenic or myopathic cause. Ten different clinical forms (DA1 to DA10) have been described, with DA1 and DA2B as the most common forms; some other forms are very rare. Beck et al (2013) suggest phenotypic overlap of DA1 and DA2B and that DA1 and DA2B may be phenotypic extremes of the same disorder.

Features shared amongst all distal arthrogryposes include consistent patterns of hand and foot involvement, limited involvement of proximal joints, and variable expressivity within families.

DA1 (OMIM#108120) and DA2B (OMIM#601680) have an autosomal dominant pattern of inheritance but de novo cases have been reported. Penetrance is highly variable in this condition so a mildly affected parent may have a severely affected child.

A proportion (~9%) of DA1 and DA2B cases are caused by mutations in the $\text{TPM2}$ gene (9p13.3, MIM190990) which encodes beta-tropomyosin, an isoform of tropomyosin, that is mainly expressed in slow, type 1 muscle fibres. The Leiden Muscular Dystrophy database (www.LOVD.nl/TPM2) and Beck et al (2013) altogether list 12 $\text{TPM2}$ mutations associated with DA (9 missense mutations, 1 small deletion and 2 possibly affecting splicing).

Molecular genetic analysis reduces the requirement for other invasive tests such as nerve conduction studies and muscle biopsy. Testing also enables a precise diagnosis in this difficult group where there is clinical overlap and a wide variety of conditions presenting with contractures, allowing clinicians to decide on appropriate management.

Service details
Full direct bidirectional sequence analysis of the $\text{TPM2}$ gene is available at BGL at a cost of £522. The $\text{TPM2}$ gene is amplified in 9 amplicons (including flanking intronic sequence, predicted branch points and both forms of alternatively spliced exons 6 and 9). This screen has a sensitivity of approximately 99%; routinely results will be available within 40 days (urgent samples can be processed within 2 weeks). Carrier testing (£190) and prenatal diagnosis is available for cases with a confirmed pathogenic mutation.

Future Developments
Mutations in the following genes have also been associated with Distal Arthrogryposis type 1 and Type 2B: $\text{MYBPC1}$ (DA1), $\text{MYH3}$ (DA1 & DA2B), $\text{TNNA2}$ (DA1 & DA2B), and $\text{TNNT3}$ (DA1 & DA2B). Testing will be available shortly for the $\text{TNNA2}$ and $\text{TNNT3}$ gene at Bristol Genetics. Considerations for future developments for this service include an NGS panel incorporating the $\text{MYBPC1}$ and $\text{MYH3}$ genes, amongst others.

Referrals
Referrals meeting UKGTN clinical testing criteria are accepted from clinical geneticists. Samples should be accompanied by a completed service proforma (please contact the laboratory). Clinical advice is available from Dr Sarah Smithson at St Michael’s Hospital, Bristol.

For more information on this service and future developments please use the contacts below.

References

Contacts
Laboratory Testing
Julie Honeychurch
Clinical Scientist
Bristol Genetics Department
Pathology Sciences
Southmead Hospital
Bristol
BS10 5NB
Tel: 0117 323 2680
Email: julie.honeychurch@nbt.nhs.uk

Clinical Service
Dr Sarah Smithson
Consultant Clinical Geneticist
St Michael’s Hospital
Southwell Street
Bristol
BS2 8EG
Tel: 0117 342 5316
Email: Sarah.smithson@UHBristol.nhs.uk
Next Generation Sequencing gene panel for Disorders of Sexual Development

Graham Fews, Birmingham

The West Midlands Regional Genetics Service is pleased to offer a diagnostic Next Generation Sequencing gene panel for 32 genes known to be associated with 46,XX and 46,XY Disorders of Sexual Development (DSD). The genes complement current testing for 21-hydroxylase deficiency (CYP21A2) and provides coverage for the majority of genes associated with Congenital Adrenal Hypoplasia.

All pathological findings are confirmed by Sanger sequencing and reflex testing of at risk individuals is available. The group has strong links with Dr Trevor Cole and the laboratory feeding into the multi-disciplinary DSD team at Birmingham Children's Hospital. Suitable consented patients may be entered for further research and functional analysis within the of laboratory Dr Nils Krone, Consultant Paediatric Endocrinologist and Senior Clinical Lecturer at the University of Birmingham.

For further information and costs please contact Graham Fews at the laboratory; 0121 627 2710 graham.fews@bwhct.nhs.uk.

### 46, XX DSD

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46, XX DSD

Disorders of Ovarian Development

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Disorders of Testicular Development

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Disorders of Hormone synthesis or action

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<td>AMH receptor</td>
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Noticeboard

The Royal Society of Medicine Medical Genetics section

The Royal Society of Medicine Medical Genetics section offers several educational meetings each academic year, providing fascinating updates in this rapidly developing area of medicine and a valuable source of external CPD points. These meetings hold appeal for those who work in clinical genetics, as well as other specialists and allied health professionals who have a professional interest in genetic medicine.

Highlights for the 2013-2014 academic schedule include ‘Genomes in the clinic’, to be held on Friday 14th February 2014, featuring an overview by Prof John Bell, discussions around the bioinformatic challenges introduced by using high-throughput sequencing technologies in routine NHS care and how to meet the educational requirements necessary to practice medicine in the new genomic era. The meeting will also be broadcast online. Apply now to avoid disappointment (www.rsm.ac.uk/genetics or scan the QR code).

Early bird rates and special rates for members are available, so if you are not yet a member, join the RSM to benefit from this and other membership perks, such as excellent value room rates, the use of state of the art library facilities and reciprocal arrangements in many clubs worldwide (www.rsm.ac.uk).

The Alan Emery prize is awarded for trainees who have published as principle author a research article in medical genetics and the section will support trainees and junior consultants applying for the prestigious RSM Ellison Oliffe Foundation Travelling Fellowship. Please contact genetics@rsm.ac.uk for more information.

We look forward to seeing you at the RSM soon.

Malta Irving (Honorary Secretary)
Huw Dorkins (Section President)

Genetics in Medicine – a booklet for early career scientists, nurses and medics

Andrew Read, Dian Donnai and Helen Middleton-Price have written the first of two booklets for a non-expert audience on Genetics in Medicine, published by The Galton Institute in association with Nowgen. This booklet - Conception and Early Life – is aimed at keen ‘A’ level students with an eye on a career in the biomedical sciences, undergraduate biological scientists, nurses and medics. The second booklet, which will concentrate on adult illnesses, including complex, common conditions, will be published in mid-2014.

For a free copy of the booklet contact:

Mrs Betty Nixon
The Galton Institute
19 Northfields Prospect
Northfields
London SW18 1PE

Or download from

Helen Middleton-Price
Director, Nowgen, Manchester

UKGTN website

The new UK Genetic Testing Network (UKGTN) website (www.ukgtn.nhs.uk) went live on 29th July 2013. The website hosts a database of tests to enable users to locate a genetic test offered through the network of member laboratories. The database includes an intuitive price comparison feature. The Gene Dossiers and Testing Criteria are easily accessible and can be filtered by specialty. A resources section provides information on UKGTN activities and outputs.

www.ukgtn.nhs.uk

Direct links to:

- Database of tests: http://ukgtn.nhs.uk/find-a-test/
- Gene Dossiers: http://ukgtn.nhs.uk/find-a-test/gene-dossiers/
- Testing Criteria: http://ukgtn.nhs.uk/find-a-test/testing-criteria/
- Resources: http://ukgtn.nhs.uk/resources/

Jacqui Hoyle
Knowledge and Communications Manager, UKGTN

Looking for a genetic test for your patient?

Download the new UKGTN guide to understanding genetic testing for rare genetic disorders
- Access the guide, go to laboratory
- Access 250+ testing criteria to help choose the right test

visit UKGTN at www.ukgtn.nhs.uk
Welcome to New Members

27 new members were accepted by the British Society for Genetic Medicine in September 2013.

Dr Rebecca Bastock ACGS
Dr Christine Bell ACGS
Dr Claire Burgoyne ACGS
Ms Alesandra Callegari ACGS
Miss Lauren Carroll ACGS
Dr Malgorzata Drozdzewska ACGS
Mr Oliver George ACGS
Miss Anastasia Ingram ACGS
Dr Laura Ions ACGS
Miss Claire Laas ACGS
Dr Claire Lambert ACGS
Miss Claire Langley ACGS
Miss Emma Douglas AGNC
Mr Aidan Doherty BSGM
Dr Suzanne Drury BSGM
Dr Richard Martin BSGM
Mr Abel Ureta-Vidal BSGM
Dr Kathy Williamson BSGM
Dr Mary Alikian CGG/SGPPH
Dr Ruth Cleaver CGS
Dr Panayiotis Constantinou CGS
Dr Jennifer Gardner CGS
Mr Alisdair McNeill CGS
Dr Shwetha Ramachandrapa CGS
Dr Katherine Schon CGS
Ms Vivienne Sutton CGS
Miss Corinna Alberg SGPPH

Direct Debit Subscriptions for 2014/2015

The membership subscriptions will be collected by direct debit during 5-7 April 2014 (see table below for breakdown for each constituent group)

<table>
<thead>
<tr>
<th>Subscription</th>
<th>BSGM only</th>
<th>ACGS</th>
<th>AGNC</th>
<th>CGS</th>
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For UK Members: Preferred option for payment is by Direct Debit but this is only available for bank accounts within the UK.

Note: Please be aware that methods of payment other than Direct Debit will incur an additional £5 charge. This is not applicable to Overseas Members.

For those members who do not pay by direct debit the Society will be contacting you shortly. Membership Subscriptions are due on 1st April 2014, all payments to be received by the end of April 2014.

Affiliate Membership of the European Society of Human Genetics

For those members who have also opted to take out affiliate membership of the ESHG an additional fee of £44 will also be collected – please note that this rate has not changed as per 2013/2014 through negotiations.

Your ESHG membership will be renewed if subscribed through BSGM unless we are notified by yourselves otherwise before the end of March 2014.
Travel awards

As part of its role as a charitable organisation, the British Society for Genetic Medicine will support the travel costs for members who wish to attend International meetings and conferences. This is subject to them meeting the assessment criteria for these awards.

Support under this scheme is available to BSGM members who were elected to the Society at least twelve months before the closing date for applications, and who are in good standing with their annual subscriptions. UK based members are not eligible for travel awards within the UK. However members based outside the UK can be considered for an award for a meeting within the UK including attendance at the British Genetic Medicine Conference.

Maximum awards are currently as follows: £250 Europe, £450 Rest of World, at the discretion of the panel.

To be considered for an award, members must have an abstract accepted for the meeting.

Travel awards are specially intended to support young investigators; therefore applicants should be younger than 35 years of age at the time of application.

The BSGM Travel Awards Panel meets four times a year, and in making awards considers the scientific value of the applications received, and also looks favourably on younger scientists. It should be noted that awards made under this scheme are not intended to cover the full cost of the proposed activity. In addition, members may not apply for an award if they have received an award within a three year period.

The deadlines for applications are:

- 1 January (midday)
- 1 April (midday)
- 1 July (midday)
- 1 October (midday)

The panel will prioritise and issue awards on scientific merit, also taking into account the juniority of the applicant. A condition of the Travel Awards is that applicants are required to submit a brief report (350 words maximum) on the activities carried out with the support of the Award. This should be submitted to Mrs Dina Kotecha (bshg@bshg.org.uk) within 1 month of the end of the visit.

Please note that, although the BSGM endeavours to ensure that travel awards are awarded to as many applicants as possible, there will be occasions where applications are unsuccessful.

An application will generally require:

- A completed application form
- A copy of the abstract being submitted to the meeting in question

Travel Award Application forms may be obtained from the BSGM Website.

BSGM 2014

22-24 September 2014, Arena & Convention Centre, Liverpool
Confirmed sessions: UK 100,000 Genomes Project, Impact of Genomics in the Developing World, New Genetic Services (UKGTN), Dermatogenetics, Ciliary Diseases, DDD Complementary Research Projects, Mutational Mechanisms, Genetic Counselling, Global Data Sharing Initiatives, Education in Genetics, Prenatal Genomics, Gene Regulation, Cancer Genetics, Molecular Pathology and Stratified Medicine, Treatment in Genetic Disorders and NIHR Grant Updates.
Conference Reports

ESHG 2013 Paris, France
Debbie Smith, Trainee Clinical Scientist, Bristol Genetics Laboratory

The ESHG 2013 congress was held at the grand Palais de Congress in Paris, France. The 4 day conference had over 2900 delegates, and over 2000 abstracts had been submitted for presentation. I was fortunate to be able to attend the ESHG conference and present a poster on my research in FSHD, and this led to some very useful networking opportunities. The conference started with a Welcome address from the President of the ESHG, Stanislas Lyonnet, who stressed the need for openness and education in Genetics, and reaffirmed that both Clinical and Research Genetics need to be promoted, and there needs to be an alliance to ensure bench to bedside translation.

The program of topics was wide and varied, and deciding which sessions to attend was a challenge. In a number of the sessions there was a strong emphasis on interpretation of exome sequencing data, some of the presentations were shared between clinical and laboratory professionals, highlighting the increased need for staff in the laboratory and clinic to work closely together. I was particularly interested in the Cancer Genetics sessions and also the Prenatal/Pre-implantation genetic screening and diagnosis presentations, and it was very interesting to hear about the latest research in these areas. Attending the conference has given me a greater understanding of the current developments in Genetics, and has also helped me to further develop my own research. I would like to thank the BSGM for the travel award which contributed to being able to attend the conference.

ESHG 2013 Paris, France
Alison Foster, ST3 Clinical Genetics, Birmingham Women’s Hospital

As a first year registrar in clinical genetics, attending the European Human Genetics Conference in Paris in 2013 was a fantastic opportunity and I am very grateful for the travel award from BSGM. I found the scientific programme exceptionally varied and interesting, and attended sessions on themes including cancer predisposition, prenatal diagnosis, epilepsies, retinal dystrophies and immunological disorders as well as a dysmorphology workshop. A session on ‘How to get published in EJHG’ was particularly helpful for those of us embarking on our careers in clinical genetics, while a completely different and fascinating perspective of human genetics was provided by an educational session on ‘A genetics history of our species’. Discussing my poster on a case of two siblings with a microdeletion causing intellectual disability with the author of the paper that first proposed a recognisable phenotype for this microdeletion was a highlight of the conference for me. After a busy four days, I found Professor Huda Zoghbi’s Mendel lecture on her work on Rett syndrome and MECP2 a particularly inspiring session on the final afternoon. In summary, ESHG 2013 was a great educational experience and I would encourage other trainees to submit abstracts for next year’s meeting in Milan.

ESHG 2013 Paris, France
James Whitworth, Clinical Research Fellow, University of Birmingham

As a clinical research fellow in with an interest in clinical cancer genetics, my first ESHG congress was an opportunity to present my initial findings, take advantage of the scientific programme for insights to help develop my work further and meets new colleagues/catch up with older ones in the ever stimulating environs of the French capital.

The starting point for my and many other gene identification studies is development of a phenotypic angle that might enhance the likelihood of variant identification. The idea to use severe (as opposed to recurrent) influenza to elucidate IRF7 as a high penetrance susceptibility factor was a simple but memorable tactic.

I plan to apply exome-sequencing techniques during my research and there were some good illustrations of how the chances of success in this area can be increased by combination with more established strategies such as linkage analysis in epilepsy, identification of homozygous areas in consanguineous families and array CGH in copy number variant analysis.

Another thing I will take away from the congress is the quality and extent of functional validation presented alongside possible significant variants identified by researchers. This not only serves to support their significance but also reveal some interesting paradigms of tumourigenesis. Mosaic PPM1D mutations associated with breast cancer but without being present in the tumours themselves are especially intriguing.

So all in all a great few days and some inspiration to get behind the lectern in Milan!
Forthcoming conferences

Venue: Stadsgehoorzaal (city auditorium), Breestraat 60, Leiden, the Netherlands
Contact: jointmeeting@routine-nijmegen.nl
Website: http://www.jointmeeting2014.com/

Dysmorphology Meeting: 19 March 2014
Venue: Poortgebouw, Rijnsburgerweg 10, Leiden, 2333 AA at the University
Contact: Dr Emilia Bijlsma
staffsecretariaat.kg@lumc.nl
Website: http://www.jointmeeting2014.com/

(AGNC) Association of Genetics Nurses & Counsellors Spring Meeting: 03 April 2014
Venue: University Hospitals Bristol, Education Centre, Upper Maudlin Street, Bristol
Contact: cath.king@ruh.nhs.uk
Website: http://agnc2014.bshgconferences.org.uk

(ESHG) European Human Genetics Conference: 31 May - 03 June 2014
Venue: Milano Congressi, Viale Eginardo (Gate 2), Milan, Italy
Contact: eshg@medacad.org
Website: www.eshg.org/eshg2012

(BSGM) BSGM 2014: 22 - 24 September 2013
Venue: Arena & Convention Centre, Liverpool
Contact: Dina Kotecha
(bshg@bsmg.org.uk)
Website: www.bsgm.org.uk

(ASHG) American Society for Human Genetics Annual Meeting: 18 – 22 October 2014
Venue: San Diego Convention Center, San Diego, CA, USA
Contact: ashgmeetings@ashg.org
Website: http://www.ashg.org/2014meeting/

In addition to the events listed above, details on other courses and conferences of interest can be found on our website: http://www.bsgm.org.uk/news-events/events/

Deadline for contributions for next issue is 30 April 2014

BSGM 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: michellebishop@nhs.net
As I write this, the first weather-induced travel disruptions are causing much grief to long-distance Christmas shoppers, and the Christmas TV ads are tempting the launch of increasingly large projectiles towards the box. This bumper edition of the ACGS section of the BSGM Newsletter sees some excellent pieces. First off, I am delighted to see that Professor Meena Upadhyaya has been rewarded for her excellent work in the field of Neurofibromatosis; the editorial office must have mislaid ones invitation to the bash down in Cardiff(!). We also have a beautiful demonstration of the value of hindsight in a most interesting article from Vikki Moye and others, who show what a difference a decade can make in sequencing results of the same VHL patient; a case of: “I can see it, now that you have pointed it out!”.

Gareth Cross and Stephanie Allen provide useful feedback on this year’s FRCPath Part 1 exam, which took on the new format of one paper of Short Answer Questions and one essay paper. It sounds as though some candidates didn’t know the difference, so marks may have been needlessly lost. Guys, it’s hard enough already: don’t make it even harder for yourselves!

We also have an interesting contribution from Polly Talley (Multiple Myeloma Conference in Dublin), plus an unintentionally and slightly controversial one from Sian Ellard, who documents the duplication of a laboratory’s efforts by clinicians wishing to investigate the possible pathogenicity of new variants. The rightly protected title of ‘clinical scientist’ implies – indeed, requires – that a CS has a degree of knowledge and experience that enables her or him to interpret the clinical significance of novel variants. Without that, we are technicians…. 

As usual, space constraints mean that some articles didn’t quite make it into this issue, including several adverts that were masquerading as articles; (don’t worry, these have been moved to the Section entitled ‘Service Developments’ in the main section of the newsletter, so all is not lost). Also missing is the article from ‘Confused of Clapham’, who heaped deserved praise on the snappy new ACGS website, but pointed out that the DNA Lab Directory is still in the rusty old CMGS web pages which means that some information is not as up to date as it might be. Rather bizarrely, one lab’s website has a home page that appears to have been hacked into by someone selling everything from bank refunds to advice on emigrating to Canada! But perhaps that is how we are supposed to top up our meagre funding these days.

On a sadder note, we have recently lost one of the stars of the modern genetic age with the death of Fred Sanger; I am assured that sequencing suites the length of the country observed a two-minute silence in his memory.

Martin Schwarz
NHS Clinical Scientist awarded prestigious international prize for genetic research

Ian Frayling

At a recent international conference in Cardiff, organised in association with the Wales Gene Park, on Recent Developments in Neurofibromatoses and Rasopathies, Professor Meena Upadhaya PhD FRCPath was awarded the prestigious Theodor Schwann prize. The prize is named after the German physiologist who identified the cells which give rise to the tumours that affect patients with neurofibromatosis type 1 (NF1). The European NF group awards the prize, from time-to-time, in recognition of outstanding scientific contributions to NF1 and Prof. Upadhaya is only the third recipient of it. The reception before the dinner when the award was presented was attended by Professor Mark Drakeford AM, Minister for Health and Social Services in Wales, who also made reference to Professor Upadhaya’s contributions to the Asian community in Wales. Also present was Professor Sir Peter Harper, who in 1987 established the Institute of Medical Genetics at the University Hospital of Wales, Meena being one of the founder members of the Institute. The conference proceedings will be published in the American Journal of Medical Genetics.

Meena has always recognised the importance of directly involving patients in research, and to this effect she has organised annual meetings of Welsh NF1 patients, facilitating interaction with them and providing updates on recent scientific and clinical developments. Thus a special feature of the Recent Developments in Neurofibromatoses and Rasopathies meeting was that patients and their carers were given the opportunity to speak on their experiences, including one Welsh patient who was a ‘Very Important Patient’: Meena had found a 90 kb deletion in this patient in the region of chromosome 17 encompassing what later turned out to be the NF1 gene.

Meena has also worked on Duchenne muscular dystrophy, Charcot-Marie-Tooth, Sotos and Prader-Willi/Angelman syndromes, as well as developing and applying various laboratory techniques to molecular diagnosis.

Meena has also worked on Duchenne muscular dystrophy, Charcot-Marie-Tooth, Sotos and Prader-Willi/Angelman syndromes, as well as developing and applying various laboratory techniques to molecular diagnosis. She presented her findings at a meeting in New York in 1990, which caused some stir amongst the attendees, and as a result she was invited to work as a visitor in Ray White’s laboratory in Salt Lake City, Utah. Meena just missed being a co-author on the paper from this laboratory which identified the NF1 gene, because she returned to the UK for her daughter’s exams.

Over the years Meena has had a most successful track record in attracting and supporting students to her laboratory, having supervised undergraduate and postgraduate students, including both PhD and MDs. She has published nearly 200 peer-reviewed scientific papers as well as editing three books on NF1 and FS1D. She has chaired several international meetings, is on the research advisory board for the Children’s Tumor Foundation in the USA, the medical advisory board for Neuro Foundation in the UK, and the management committee of the NF Euro Group. In 2010, Meena was the first recipient of the Inspire Wales Award for Science and Technology, and in 2011 she received from the Welsh Government a Recognising Achievement Award for her contributions to Medical Genetics.
Can you spot the mosaic mutation?
A case for repeat sequence analysis

Vikki Moye, Martina Owens and Sian Ellard on behalf of the Birmingham, Cambridge, Dundee, Exeter, Leeds and Oxford labs

In 2004 a 9 year old girl with a unilateral phaeochromocytoma was referred to Lab A for VHL mutation analysis. Sanger sequencing on a gel-based ABI377 DNA sequencer did not detect a mutation and nor did subsequent capillary sequencing of RET, SDHB, SDHC, SDHD, SDHAF2, TMEM127 and MAX. In 2013, aged 18 years, she developed a paraganglioma. The VHL gene was re-sequenced in Lab B using ABI3730 capillary sequencing and a mosaic c.250G>T (p.Val84Leu) mutation was identified. This mutation has previously been reported in patients with Von Hippel-Lindau syndrome (Crossey et al JMG 1995, Abbott et al AJMG 2006 and Leonardi et al Annals Hum Genet 2011). The level of mosaicism within the leukocyte DNA sample was estimated at ~20%.

Blind inspection of the sequence electropherogram from 2004 (see figure) by multiple scientists did not detect the mutation due to high background (although it was possible to see it once the mutation location was revealed). The DNA sample was distributed to four additional laboratories who offer testing for phaeochromocytoma and paraganglioma. All six laboratories could detect the mosaic mutation using their standard capillary-based Sanger sequencing protocols (estimated mutation level 15-40%). Next generation sequencing in one laboratory detected the mutation and allowed more accurate measurement of the mosaicism from read counts as 19% (57/308 reads).

The improved sequence quality is a direct result of the capital investment in NHS Genetics labs following the White Paper Our Inheritance, Our Future – Realising the potential of genetics in the NHS (2003), improvements to sequencing chemistry and analysis software packages. The message for clinicians is to consider repeat testing for patients with a high likelihood of a genetic diagnosis in whom sequence analysis using obsolete technology failed to detect a mutation.
ESH (European School of Haematology)  
International Conference on Multiple Myeloma. Dublin, Ireland 4-6 October 2013

Polly Talley, Sheffield Diagnostic Genetics Service.

Multiple Myeloma (MM) is a neoplastic condition of plasma cell precursors associated with overproduction of a monoclonal immunoglobulin. MM is the seventeenth most common cancer in the UK, equating to approximately 5,000 new patients being diagnosed with myeloma in the UK per year. Although huge advances have been made in the treatment of myeloma over the past two decades and it is now regarded as highly treatable, myeloma remains incurable for the vast majority of patients who develop the disease. The only fully curative treatment for myeloma is allogeneic stem cell transplantation, a procedure that carries an extremely high mortality rate and is thus reserved for a small number of eligible individuals.

Myeloma is a genetically complex disorder requiring multiple genetic changes in numerous cellular pathways that have the ability to deregulate the intrinsic biology of the plasma cell. Hyperdiploidy is seen in 30-40% of patients, often involving gains of the odd numbered chromosomes. Non-hyperdiploid patients are frequently associated with rearrangement of the IGH gene on chromosome 14, with five main partner genes shown to upregulate one of the Cyclin D genes. Critical deletions and monosomy of specific chromosomes are also seen, some of which are thought to occur with disease progression. Evidence suggests inherited genetic variation can provide a genetic predisposition to the benign precursor condition monoclonal gammopathy of undetermined significance (MGUS) which can progress to myeloma as well as known epigenetic factors which can contribute to the disease.

The conference organisers, Dr Mateos (Salamanca), Dr Palumbo (Turin) and Professor Morgan, Consultant Haematologist from The Royal Marsden Hospital, London presented a carefully thought through conference covering many aspects of this interesting, but extremely complex disease.

The conference followed a number of themes: the first day covered the genetic changes associated with MM, with day two covering more of the clinical aspects of the disease, from staging and risk stratification, to treatments, therapeutic strategies and side effects, and then finishing with day three focusing on other monoclonal gammopathies and related disorders.

Technology played a big part in the conference, not only were a huge number of participants photographing slides and recording talks, but the organisers had made use of a very neat app that allowed questions to be texted through to the speakers at the end of the talks, projecting the questions for all to see!

Although this conference had a more clinical leaning than conferences I have previously participated in, this offered excellent context to the importance of genetics and the need to offer a more uniform and consistent approach to the genetic diagnosis of MM. It is obvious that a deeper and clearer understanding of the genetic abnormalities and their role in specific pathways may offer potential routes for drug development, targeting those specific pathways. This could enhance the ability to offer a stratified and personalised medicine approach to treating myeloma patients.

The conference itself was held in a beautiful hotel and conference centre on the outskirts of Dublin amongst rolling countryside and a golf course. However, I couldn’t get that near to Dublin without venturing into the city and the very famous Temple Bar area for at least one pint of Guinness and little live music!

I am extremely grateful to the ACGS for the travel bursary which allowed me to attend this excellent, informative and very useful meeting.
Feedback on the FRCPath Part 1 written examination 2013

Gareth Cross, Nottingham University Hospital NHS Trust, & Stephanie Allen, Birmingham Women’s NHS Foundation Trust.

There were 14 candidates who sat the Part 1 FRCPath written examination held on 26 March 2013. Nine candidates were successful giving a pass rate of 64%.

This was the first year that the Essay Paper 1 had been replaced by a paper of short answer questions (SAQs). The paper consisted of 20 SAQs to be attempted in three hours, which approximates to nine minutes per question. Each SAQ has a stem and six sub-questions, is worth 20 marks in total, and is focused around a particular subject area (eg cystic fibrosis, array CGH, colon cancer, GWAS). This year, seven of the SAQ questions were common to the cytogenetic and molecular papers.

The SAQ questions are criterion-marked against an explicit model answer, and no other marks are awarded for additional information. If a defined number of facts are requested (e.g. State two causes of… …), only the first two responses are marked. Many of the questions can be answered by a single word or phrase, and candidates requiring more than single word or phrase responses are answerable in a single sentence or a small number of sentences. Given the tight time schedule for completing the paper candidates shouldn’t feel the need to write in complete sentences. They should also be aware of the number of marks awarded to each section and to divide their time spent answering each section accordingly.

Candidates should remember, however, that the second written paper is an essay paper, requiring a structured, coherent argument to be presented. Note-form answers are penalised. For both papers, candidates should beware referring to acronyms without explanation. It is also important that terminology is used appropriately, and that details such as gene names and drug names are spelt correctly.

For the Essay paper 2, candidates are required to answer four out of five questions. The paper is marked using a closed marking system:

- 15 – maximum – excellent pass – top mark = 60
- 14 – clear pass
- 13 – pass
- 12 – borderline fail
- 11 – clear fail
- 10 – minimum – bad fail

The pass mark for the essay paper is 50, and the SAQ paper is marked using an Angoff scoring system. The marks are combined from both papers and can compensate if 48 - 49 on essay paper and a corresponding surplus on other paper.

2. Describe Preimplantation Genetic Diagnosis (PGD) and Preimplantation Genetic Screening (PGS). You have been asked to set up laboratory testing for PGD. What testing methodology would you use, and what are the important factors to consider when developing and running the service.

This question was answered by 11/14 candidates. They were expected to distinguish between PGD and PGS, and then describe the processes. There should then have been brief descriptions of the testing methodologies available for PGD which should have included chromosome abnormalities (arrays / FISH) in addition to single gene disorders. A discussion should have followed including factors such as proximity between the testing laboratory and the rest of the service, links with the clinical genetics service, possible contamination risks, risks from allele drop out, validation requirements, required turnaround time, staffing considerations, success rate etc.

1. Several large scale genomic studies have gained prominence recently. These include the DDD (Deciphering Developmental Disorders), the ENCODE (Encyclopaedia of DNA Elements), and the 1000 genomes projects. Discuss the aims of these studies, and how the results of these, and others, will provide important resources for array, whole genome or exome sequencing-based diagnostic services.

This question and Q5 were the least popular questions, being answered by 10/14 candidates. Detailed knowledge of all three projects was expected, and these should have been related to service provision. A common reason for lost marks was the lack of detail supplied, or inability to describe one of the projects. Marks were also lost for merely listing a series of thoughts, instead of drawing together points in a reasoned argument. For example, the large amount of non-coding, but functional control sequences discovered in the genome by the ENCODE project might have been used to argue for the eventual adoption of WGS rather than WES.
3. Discuss the importance of de novo mutations in human genetic disease and to service provision (do not include sporadic cancer). Include in your discussion: different types of mutation, mechanism, incidence, predisposition, discovery, pathogenicity.

This question was answered by 12 candidates. The answers were expected to cover a broad range of knowledge with plenty of examples, as suggested by the question. For example, these might have included a discussion of germ line versus somatic mutations, mosaicism, imprinting defects, recurrence risks, the effect of parental age on mutation rate, predisposition of sequences (e.g. triplet repeats) or chromosome architecture (e.g. CNVs) to mutate. The use of WES to detect these mutations and potential problems in calling the pathogenicity of any detected variants might have been included.

4. What are the standards which a genetic laboratory should meet to ensure it is providing a high quality service? Explain why these are necessary

This was the only question that was common to both the molecular and cytogenetic papers. It was also the most popular question – being answered by 13/14 of the molecular candidates. It should not have been a problem for anybody familiar with the CPA/ISO15189 standards, but many candidates had problems in answering this on a broad enough front. Also, candidates tended to not answer the second part of the question. Marks were lost for failure to refer to specific areas such as quality management, quality manual, quality policy, facilities, users, validation, audit, quality control, etc.

5. What is the clinical utility of providing a service for detecting acquired mutations in non-small cell lung cancer? Discuss the type of service you would set up and the issues you might encounter.

This question and Q1 were the least popular questions, being answered by 10/14 candidates. Candidates were expected to understand and describe the clinical context of the testing, and the significance of EGFR mutations on the decision as to whether to treat patients with gefitinib. This should have been explained with reference to cellular pathways. Candidates were also expected to have some idea of the proportion of patients with these mutations. Further marks were awarded to information on ALK rearrangements x crizotinib. There should then have been discussion on the interaction required with the departments supplying the samples, sample size and quality issues, the testing methodologies used, validation, turnaround times, etc. The better answers included the potential use of cell-free DNA and the use of next generation sequencing to increase sensitivity.
Do clinicians want to see the evidence used by laboratories to classify the pathogenicity of novel variants?

Martina Owens and Sian Ellard, Exeter

The short answer is YES!

Interpreting novel sequence variants of uncertain pathogenicity constitutes a significant workload for both clinical scientists and requesting clinicians. The CMGS Best Practice Guidelines published in 2007 (review in progress, 2013) (http://cmgsweb.shared.hosting.zen.co.uk/BPGs/Best_Practice_Guidelines.htm) state that “it is not essential to document all the lines of evidence obtained in the report, however complete records must be stored in the laboratory”. In line with this, we designed a form to record the evidence gathered for each variant and stored it on our LIMS. Then a discussion with one of our local Clinical Geneticists revealed that many of the investigations undertaken by the laboratory to investigate pathogenicity (eg literature reviews and database searches) were being replicated by the clinician. We decided to start issuing the pathogenicity information form to clinicians and have sent these forms out with the laboratory report for more than two years.

A recent user satisfaction survey generated a low response rate (12%) but all 11 responders told us that they had found the form useful and the content appropriate for their needs. One clinician highlighted that suggestions for further studies (eg. mRNA analysis) should only be indicated if the laboratory is prepared to perform these studies or to indicate where these might be carried out (which seems very reasonable). Another user requested some explanation about the in silico tools so we have added a webpage to our website (www.rdehospital.nhs.uk/prof/molecular_genetics/tests/Silicertools.html). Finally (and the reason for writing this article), one person commented “Extremely helpful. I wish all labs did this....”
Editorial

In this Association of Genetic Nurses and Counsellors (AGNC) section of the newsletter we have details of beginnings and endings.

Heather Skirton writes about exciting moves to set up a Registration system for genetic nurses and counsellors across Europe following the system pioneered in the UK. Diana Scotcher gives information about new guidelines on the timing of eligibility to register as a genetic counsellor covering those from science and nursing routes. And Anita Bruce, in her AGNC update, gives details about the AGNC position statement on opportunistic genome screening and incidental findings.

The endings include grateful thanks to Carolyn Owen who stands down after 6 years as AGNC Chair and a tribute by Sue Kenrick to our much loved and respected colleague Ann Kershaw, who is retiring after 24 years working in genetics.

Vicki Wiles, Principal Genetic Counsellor, Cambridge

Report from the European Board of Medical Genetics (EBMG) - Nurse and Counsellor Division

Heather Skirton, Professor of Applied Health Genetics, Plymouth and Chair of EBMG

Members of the EBMG Genetic Nurse and Counsellor Division working on the registration plan in Taunton, February 2013. Left to right: Milena Paneque (Portugal), Ramona Moldovan (Romania), Ingrid van Kessel (Netherlands), Heather Skirton (UK), Christophe Cordier (France), Inga Bjornevoll (Norway), Clara Serra (Spain).

I am pleased to report that we continue to make significant progress towards the goal of establishing the registration system for genetic nurses and counsellors in Europe. The European Board of Medical Genetics was established by the European Society of Human Genetics (ESHG) in June 2012 and comprises three divisions, for 1) genetic nurses and counsellors, 2) medical geneticists and 3) clinical laboratory geneticists. Medical genetics is recognised as a speciality in Europe, but there was no system for recognition or registrations of counsellors or laboratory geneticists. The first task of the EBMG was to establish appropriate systems to ensure standardisation of education, training and practice across Europe.

The minimum standard of education for genetic counsellors is the Master’s degree in genetic counselling, and there are five programmes approved by the EBMG that conform to the required European core curriculum. These include the programmes run by Cardiff and Manchester universities in the UK. However, as there are many experienced genetic nurses and counsellors working in Europe who will not have had access to MSc programmes in the past, the registration system does include a grandfather clause, which will be open for five years.

The UK is the only country in Europe with an existing national registration system, but of course there are genetic counsellors working in Europe who have registered in other countries such as the US, South Africa or Australia. Those practitioners who have registered under a recognised system elsewhere can apply for European registration without submitting a portfolio. The UK system was assessed and is recognised by the EBMG.

The new registration system for genetic nurses and counsellors was launched at the Opening Ceremony of the ESHG meeting in Paris in June, 2013. We opened the application process for registration at that time and have had 30 applications this year (applications now closed). Those who are eligible have been asked to provide their portfolios by 15 January, and the division will meet in person in February to assess the applicants for registration. This is very much a work in progress and we are learning as we go through this process for the first time.

For more information, please go to the EBMG website [https://www.eshg.org/408.0.html].

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Genetic Counsellor Registration Board (GCRB) update

Diana Scotcher, Principal Genetic Counsellor, Manchester, Co Chair GCRB

The vote for Accredited Voluntary Registration (AVR)

The GCRB and the Joint Committee on Genetic Counsellor Regulation (JCGCR) are making good progress in gathering evidence to complete an application for Accredited Voluntary Registration (AVR) for genetic counsellors with the professional Standards Authority (http://www.professionalstandards.org.uk/). There is considerable support for the regulation of genetic counsellors from the British Society for Genetic Medicine (BSGM), the Clinical Genetics Society (CGS) and Genetic Alliance UK.

The JCGCR is currently seeking funds to support this application process, which must be supported by a fee of £12,000. The GCRB would like to thank individual and departmental donations which now total £7000. If sufficient funds are raised from other sources, the GCRB will be in a position to apply for AVR.

Once we have sufficient funds to proceed we will hold a vote amongst GCRB registered genetic counsellors. The JCGCR are producing a video with further information about AVR and this will be distributed at the time of the vote. Please continue to follow the JCGCR on Twitter@JCGCR and to talk to your lead GC and GCRB to understand the importance of regulation and the pros and cons of AVR.

New GCRB website

The GCRB website is being developed to improve the patient interface. Currently it includes information for prospective genetic counsellors and professionals. However, as the voluntary regulator for genetic counsellors, the GCRB website must also contain information for patients; including mechanisms for patients to raise concerns about GCRB registered genetic counsellors. The GCRB website will be developed to improve information for genetic counsellors, for other health professionals and for patients.

Registration fees

Fees are currently paid every five years when registration is renewed. In 2014 the GCRB plan to move to annual payment of fees using electronic banking, whilst, at least in short term, registration will continue to be renewed every five years. Annual fees will increase to bring them into line with fees paid to other equivalent health professional bodies. More information will be available at the time of the AVR vote. The increase in fees will improve the financial stability of the GCRB, which will be critical in the future. The GCRB have requested a financial review and have a business plan in place to meet AVR costs and our long term financial needs.

Changes to timing of eligibility to register for Set B from 2016

For some time the GCRB have been aware that there is a difference in the timing of when applicants in Set A and Set B are eligible to apply for GCRB registration. Both sets must have two years experience in a genetic counselling post. However, those in Set A (who have an MSc in Genetic Counselling) can submit their Notification of Intention to Register Form two years after they receive formal notification from the relevant university confirming completion of the MSc degree. Set B applicants (who have a nursing or midwifery qualification) may submit their Notification of Intention to Register Form when they have completed 2 years experience, irrespective of when they gained the other qualifications that make them eligible to register as genetic counsellors—namely completion of training in counselling skills, and completion of an academically accredited course in the science of human genetics.

The GCRB have given considerable thought to these differences, and have discussed the issues with the AGNC committee and the Lead Genetic Counsellors. Patient safety is central when planning the registration of genetic counsellors, as is the equity of both groups.

From 2016 Set B applicants will be eligible to submit their Notification of Intention to Register Form two years after they have received formal written communication that they have successfully completed both the counselling and the science courses, and as previously when they also have two years experience in a genetic counselling post. There will be no changes for Set A applicants. More details will be on the GCRB website.

Plagiarism software from 2015

University and other academic institutions are increasingly asking students to put written work through software to detect plagiarism before or on submission. The GCRB are going to bring the registration process in line with this practice from 2015 by asking applicants for registration to review the case studies and essays using a software package to detect plagiarism.

More details will be on the GCRB website.
The AGNC are continuing to work closely with the Genetic Counsellor Registration Board (GCRB), Joint Committee on GC Regulation (JCGCR), GC Training Panel (GCTP) & Lead GC Group, focusing primarily on regulation, registration and training. A joint meeting with the chairs of these groups was held in June and future meetings are planned to ensure on-going collaboration and involvement in the issues currently impacting on our profession.

Changes to the committee
Over the last few months the committee composition has significantly changed. Carolyn Owen completed her six-year term on the AGNC at the end of August. We would like to thank Carolyn for her hard work and efforts. Her professionalism, enthusiasm and never ending sense of humour will be greatly missed on the committee.

In September, after much thought, Donna McBride stepped down from the committee. We would also like to thank Donna for her time and hard work.

Nominations for a new committee member closed in November. We were delighted to receive six nominations from the membership and look forward to welcoming our new committee member in December. As other committee members will be completing their six-year terms in 2014, there will be another election shortly. Serving on the committee is an exciting challenge. We would encourage AGNC members to consider putting themselves forward for nomination in future.

In November, Liwsi-Kim Protheroe-Davies leapt from the frying pan into the fire when she took on the role of AGNC treasurer. Peter Marks was elected in April 2013 and has been thrown straight into the role as AGNC secretary. We also welcome Claire Giffney as the co-opted Trainee and New GC representative to the committee. Claire has already developed terms of reference for the New GC group and we are sure will be an excellent representative for new members to our profession.

In light of these changes, the AGNC committee now comprises:

Chair: Laura Boyes
Vice Chair: Anita Bruce
Secretary: Peter Marks
Treasurer: Liwsi-Kim Protheroe-Davies
Members: Oonagh Claber
Cath King
Vacant position
Trainee/New GC Rep: Claire Giffney

Contact details for the committee are on the AGNC website and members are very welcome to contact any committee member if they have any issue they are concerned about.

Website
The AGNC and BSGM websites have undergone substantial redevelopment. The new AGNC website was launched in spring 2013. Thank you very much to Liwsi-Kim for her hard work and patience on this challenging project. We are sure everyone will agree that the new website is a vast improvement and we hope this will much more effectively meet the needs of the membership.

In light of the changing roles on the committee Phil Leonard (Birmingham) has kindly agreed to take on the mantle of AGNC webmaster. If you have any queries, comments or suggestions for the AGNC website, please contact Phil.
AGNC News in Boston, USA in October. We look forward to reading about their experiences at these meetings in future editions of the BSGM newsletter.

Spring meetings
The next AGNC Spring meeting will be hosted by Bristol on 3 April 2014. This promises to be an interesting one-day meeting and calls for abstracts will be announced shortly.

The AGNC spring meeting will merge with the European Society Human Genetics (ESHG) and British Society Genetic Medicine (BSGM) meetings in Glasgow in 2015 to incorporate a strong psychosocial component and showcase genetic counselling in the UK while supporting the significant developments towards European registration for GCs.

Opportunistic Genomic Screening
In 2013 the American College of Medical Genetics published guidelines advocating obligatory testing and disclosure of incidental findings within exome and genome screening. In response to these recommendations, the AGNC formed a working party led by Anna Middleton, to prepare a position statement on elements that should be considered should opportunistic genomic screening be implemented in practice in the UK. The position statement is available on the AGNC website.

http://www.agnc.org.uk/media/768382/final_agnc_position_statement_on_opportunistic_genomic_screening.docx

The AGNC would like to thank the working party for their hard work on this important document.

Genetic Counsellor Training
The Department of Health training scheme for GCs was highly successful but has now ended. The Genetic Counsellor Training Panel (GCTP) continues to explore possible avenues for GC training. The GCTP would urge anyone with a Band 6 to update their validation as a training centre for the post to be monitored and supported by the GCTP.

Travel awards
Two AGNC members have recently been awarded travel awards. Caroline Benjamin received a £150 award to attend the ISONG meeting in Bethesda, USA in October and Sian Nisbet was awarded £300 to present at the ASHG conference.

AGNC News Editor

Deadline for contributions for next issue is 30 April 2014
Vicki Wiles
Principal Genetic Counsellor
Medical Genetics
Box 134, ATC, Addenbrooke’s NHS Foundation Trust.
Cambridge CB2 0QQ
Tel: 01223 216446. Fax: 01223 217054
email: vicki.wiles@addenbrookes.nhs.uk; vicki.wiles@nhs.net
Ann Kershaw, Consultant Genetic Counsellor, retires after 24 years in Clinical Genetics

Sue Kenwrick, Principal Genetic Counsellor, Cambridge

Ann came to genetic counselling with a wealth of health care experience having trained as a nurse at Guy’s Hospital, becoming a family planning sister and then health visitor. After seeing a talk by Clare Davison on the awesome power of Genetics she saw the light and applied for a job in Clinical Genetics at Addenbrooke’s Hospital. She almost didn’t come for the interview as she had clinical commitments that day and, in typical Ann fashion, put the patient first. Fortunately for the profession, she joined Maggie Smith and Margaret van Altaan to become what was then a Clinical Nurse Specialist on April fool’s day in 1989. Today’s genetic counsellor (GC) would hardly recognise the role as it was then. There was the preclinic ‘introductory’ call, changing the paper on the examination bed, various weights and measures, and generally smoothing the way for the Clinical Geneticists (even making tea for one consultant on arrival at clinic). Of course it wasn’t long before it was recognised that Ann’s talents were underused and with the encouragement of Martin Bobrow and Jo Whittaker in the Department there was a move towards GCs in Cambridge taking on more clinical responsibility.

Martin Bobrow says of Ann:

“Ann’s clear vision, her friendly but determined view of what patients needed and her sheer competence steadily won everyone over.”

Ann has a knack for seeing the writing on the wall and she knew that careers for health professionals would become increasingly academic. Despite being a busy mother, she had started an Open University degree, even before joining the Department. She later went on to do a Masters degree and was one of the first GCs to embrace registration. When she began counselling patients there was no structured training and she was on a steep learning curve. She remembers writing “fragile sight” in her clinical notes. Learn quickly she did, earning the trust and respect of her clinical colleagues, pioneering the establishment of GC-led consultations in Cambridge.

Her genetic knowledge was boosted by attendance at BSHG meetings and in 1990 in Newcastle she met other GCs who were keen to advance the profession (She also had to buy a BSHG sweatshirt to sleep in, it was so parky) and was part of the working party that met to discuss a process of professional registration for GCs.

Ann has been GC lead since 1995 and became a consultant GC in 2008. Her management style is to lead by example, demanding high standards of herself and her team. She has a ‘can do’ attitude to any new challenge and is unafraid of change especially where it will benefit patient care. For example, she established the PICS (patient information collation service) to streamline the patient pathway and make better use of clinical time. She values having GCs from different backgrounds, providing opportunities and encouragement for everyone to grow and progress. She steers her team with calm professionalism and also fun, having a sharp, and slightly wicked, sense of humour. Unafraid to look daft, in the Christmas panto she has been a wicked stepmother, a lion (although the costume did make her look more like a chicken), an evil magician and a rat. She makes an exceptional ‘baddie’ being blessed with the Kershaw cackle.

Early on in her GC career Ann developed a strong interest in Huntington’s disease, developing a multidisciplinary clinic and working with the HD consortium and Euro HD. Her commitment and care for HD families is inspirational and barely a day goes by without a patient, relative or carer ringing her for advice or a sympathetic ear.

Ann has many achievements to cherish in her career but she tells us she is most proud of the cohesive GC team that she has developed at Addenbrookes. When we moved to the Treatment Centre, we had to pop our heads up over partitions in our open plan office. Ann quipped that we were her meerkats (creatures that also have a matriarchal society) and like a good mother meerkat she has defended our interests fiercely. We will miss her terribly but she has brought us up to be independent, we know she will keep in touch and we will do our best to keep her proud of us. SIMPLES!
Editorial

Natalie Canham, KGC

Although this edition will not be published until after the detritus is cleared away, I am writing my editorial under Christmas lights and tinsel. While this season of course means different things to different people, for many, generosity is a major part. Appropriately enough, this issue features a host of reports from people benefitting from the largesse of CGS – and by implication of you lot. We have the excellent prize-winning student essay from 2013, by Laura Staskute, reports from medical students travelling overseas on elective, and doctors coming to our shores on international scholarships. The advertisements for the 2014 essay and international scholarships have recently been published on the CGS website, and you should encourage suitable individuals to apply.

Of course, people from within CGS are also able to persuade the Society to part with some cash – SpRs in particular are encouraged to apply for bursaries for travel to conferences, and with the 2014 CGS conference occurring in Leiden, the time could not be better. We have a report from Vinod Varghese from Cardiff on his time in Bangalore, which was also supported by CGS.

Shane has once more shared his knowledge of social media, and I would encourage those of you who partake in twitter, Facebook or LinkedIn to get yourself on those pages and hooked up with CGS. It is, of course, the future of medicine, genetics, communication and the world, and it would be a good idea to get in at the ground floor – or at least before the lift goes so high you cannot reach the button. I realise that many people regard these organisations with horror, but as with so much in genetics, it is probably a good idea not to get left behind by new technology.

*Disclaimer* It is unlikely that GCHQ or the NSA will have much interest in us as a group, but there are no guarantees......

As I am sure all of you have experienced, genetics has suddenly become of mainstream interest, with the BRCA genes of course leading the way. Angelina Jolie has, apparently single-handedly, vastly increased the number of referrals to our departments, and NICE have expanded the numbers of those eligible for testing – without, of course, increasing the testing budget. The 100k Genome project, widely available exome sequencing, mainstreaming of genetic testing, and the direct-to-consumer genomics companies are likely to provide us with multiple, and difficult referrals for a long time to come. The death of Clinical Genetics as an entity is frequently trumpeted, but personally, I think it is more likely that we will need to expand rapidly, as soon as it is recognised that it is not possible for all non-genetics doctors to be expected to comprehend genome results, the implications of a VUS, or exactly what SNPs are. While there are, of course, individuals with this knowledge, I would still much prefer that my GP was an expert in common conditions, leaving the more esoteric information to someone specifically trained in the appropriate area.
Prize-winning Student Essay 2013
Why will I need to know about genetics in my future practice?

Laura Staskute, University College London Medical School

Introduction
Human genetics has made extreme progress in recent decades, coming up with new, quicker and cheaper technologies for diagnostics and genome sequencing. New research fields, such as pharmacogenetics and predictive medicine, are evolving\(^1\), while the quantity and complexity of knowledge gained from genetic testing poses a new challenge to the UK National Health Service\(^2\). The reduction in costs, increased availability of genetic testing and the sheer popularity of this field in the media means that clinicians are facing the need to be able to interpret the test results and advise the patients accordingly. In addition, the number of new therapeutic targets that genetics is now able to offer has led to the proposals of mainstreaming genetics in medical practice\(^3\). Inevitably, this is going to pose a direct challenge to every health professional, be it a generalist, sub-specialist or a specialist, and questions have been raised about how their understanding of genomic data could be improved\(^4\). Therefore, in order to review why I (or every newly qualified clinician) will have to know about genetics in my future practice, I would like to discuss the paradigm shift which has recently occurred in genetics (moving the focus from rare to more common disorders), the mainstreaming of genetics in clinical practice and the changing public expectations for a competent clinician.

Single-gene disorders
Historically, single gene (otherwise known as ‘Mendelian’) disorders make up the field of genetics which most of research has been carried on. Although on their own Mendelian disorders are rare, taken as a whole they constitute a significant healthcare burden\(^5,6\). As the Chief Medical Officer for England noted in 2009, there are currently around 3 million patients with a rare disease in England alone\(^7\).

At the moment, both the NHS and other dedicated institutions can offer tests for over a 1000 of diseases in this category, including cystic fibrosis, polycystic kidney disease (subtypes 1 and 2), Huntington’s disease and others\(^8,9\). The value of testing is not limited to the diagnosis itself. In fact, it now enables the families at risk make reproductive decisions in the ante-natal family clinics (for example, with the help of pre-implantation diagnosis\(^10,11\)). What is more, families are also able to adjust their lifestyles in the post-natal period, so as to prevent disease development before it even manifests clinically\(^12\), as in the case of phenylalanine-restricted diet in phenylketonuria\(^12,13\). Therefore, with the aim of preventing morbidity and improving the care of such patients, healthcare professionals should have a key role in explaining the testing, diagnosis and implications of such disorders to the affected individuals and their family members\(^9\).

Genetic subtypes of more common diseases
In addition, a number of more common diseases have now been discovered to have a genetic subtype. For instance, there are genes (BRCA1 and BRCA2) responsible for hereditary breast-ovarian cancer syndrome. Although the genetic form of this disorder accounts for only ~5% of total cases of breast cancer, increased MRI surveillance and prophylactic surgery (mastectomy and/or oophorectomy) are offered according to the NICE guidelines, and have been shown to effectively reduce the risk of developing breast cancer\(^14\).

Likewise, Collins and Guttmacher\(^9\), describe a theoretical case example, whereby the knowledgeable clinician picks up on the family history of a patient and reveals a family with hereditary non-polyposis colorectal cancer. A mutation in mismatch repair gene MLH1 is found, which is known to carry increased risk of colorectal cancer, endometrial cancer or both in future\(^15\). This enables the doctor to offer the patient annual colonoscopy, pelvic examination and transvaginal ultrasound, hopefully ensuring early detection and improving the patient’s survival.

In summary, these examples show that doctors should be competent in picking up the genetic subtypes of more common diseases, as clinician’s skill to recognise the mentioned cases may have a direct impact on their patient’s outcome.

Paradigm shift
Recently, Selkirk et al.\(^15\) have argued that the technical advances in genetics have shifted the focus from rare single gene disorders onto more common multifactorial polygenic diseases, leading to a major paradigm shift in the field of genetics. Consequently, rather than being managed by specialist clinical geneticists, certain inheritable conditions are increasingly being detected and looked after from within their ‘home’ specialties. Examples include inherited bleeding disorders and thrombophilia disorders (cared for by haematologists), neurogenetics (cared for by neurologists), paediatrics (looked after by both generalist and community paediatricians)\(^16\). Arguably, by integrating genetics and genomics into their practice, clinicians in all medical specialties could help equalize the current genetics service provision across the UK and ensure better patient access to better care\(^16\).
Mainstreaming of genetics in medical practice

Furthermore, a recent report on ‘Genomic technology in healthcare’ by the Human Genetics Strategy Group\(^\text{17}\) argues that the NHS would benefit from adoption of genetics and genomic technology into mainstream medical practice. The authors suggest that genomics would not only allow more accurate diagnosis and therapeutics decisions to be made, but would also enhance disease prevention, improve disease risk prediction, as well as allow better control of infectious disease outbreaks.

The cost of whole genome sequencing has recently decreased from millions to below a thousand pounds\(^\text{18}\) and in future could potentially be offered universally. Mainstreaming of genetics could both improve the patients’ outcomes (by providing the right treatment at the right time) and ensure the cost-effective running of the NHS. Besides, the National Institute for Clinical Excellence (NICE) argues that it would have a positive public health impact\(^\text{19}\). To sum up, it is important that healthcare professionals are aware of the potential central role that genetics and genomics would take up during the time of their practice.

Challenges faced by the NHS and increasing public expectations

On the other hand, some authors claim that while the advances in DNA sequencing technologies have brought down the costs and time required for genetic testing, they have also generated a vast quantity of complex genomic information, not all of which can currently be understood and which may include incidental findings of unknown significance\(^\text{2}\). Inevitably, such data poses a new challenge to the NHS and brings doubt not only about the therapeutic options per se, but also about ethical, social and legal issues\(^\text{2}\).

One way in which doctors could minimise the potential harm that incidental findings might cause is by taking part in designing and following the guidance and protocols relating to genome sequencing. A potential caveat, however, is the availability of the so-called “direct to consumer testing”. One example is 23andMe, a private company which for only $99 offers its customers to order online a home testing kit for approximately 960,000 specific single nucleotide polymorphisms (SNPs) (equating to nearly personalised 200 traits) using the technology of DNA microarray and cells of customer’s saliva. The fact that such testing kits are becoming readily available means that the public interest in the field and concern about their health is likely to rise. Consequently, all doctors, especially those working in primary care, should prepare for being approached and questioned about the use and benefits of such testing kits by their knowledgeable patients, and have guidelines which they could refer to in case of doubt\(^\text{4}\).

Lack of training in genetics and its implications

One major problem for current and future healthcare professionals is the relative lack of knowledge and training in this potentially specialist field.

There have been numerous studies\(^\text{19,20,21,22}\) in which both qualified doctors and medical students reported or were found to have inadequate or only marginal training in genetics, resulting in their lack of confidence in this field, patient referrals to someone with a better knowledge base, increased waiting times and later diagnosis. Therefore, the Education Committee of the European Society of Human Genetics (ESHG) and the experts of the EuroGentest project have recently prepared core competences in genetics recommended for doctors across Europe which would allow them to effectively and responsibly integrate genetics into their practice\(^\text{23}\). Such guidance on skills would hopefully help improve clinicians’ confidence and prevent the delay in effective healthcare services provision which may have serious implications not only for the affected individual, but also for his family members.

On the other hand, although genetics might appear as a highly complex field to the clinician, what the patients actually need is a competent, knowledgeable doctor. For instance, in an American study which surveyed the experiences of individuals and families with genetic conditions when facing their healthcare providers, the major problems identified by the patients related to lack of reassurance and direction from their health provider rather than the doctor’s unfamiliarity with their particular condition\(^\text{24}\). Patients claimed they had felt that “doctors are afraid when they find out [the diagnosis] and prefer to refer us to another medical professional” or that “they [doctors] could have directed me to websites and other support groups instead of having to stumble upon things on my own.” Furthermore, as much as 64% participants reported receiving no genetics-education materials from their providers. It is unacceptable that these crucial opportunities for patient education and involvement in their own care are missed due to physician’s perceived lack of confidence in such an important part of their practice.
The emergence of personalised medicine

Last, but not least, it is important to mention the concept of personalised medicine, defined as “the use of genomic and other biotechnologies to derive information about an individual that could be used to inform types of health interventions that would best suit that individual”. In addition to its key relevance to cancer treatments, such principle of therapy customisation can even be applied to the particular infectious strains possessed by the concerned individual. For instance, maraviroc is only effective in HIV patients infected with the CCR5 tropic strain.

However, although personalised medicine seems very promising in terms of its potential to control nearly any type of pathology, there have been numerous criticisms of it. One interesting idea is that personalised medicine assumes that “everyone is a potential patient” and takes away the responsibility for ill health from both the individual and the society. It is critical that newly qualified clinicians keep up with this debate and understand the scope for benefits, as well as the potential risks associated with the very exciting approach that personalised medicine may offer in the near future.

Conclusion

In conclusion, recent technological achievements in genetics and genomics are likely to revolutionise the current practice of medicine. Not only has there been in a major paradigm shift from rare single gene disorders to more common multifactorial diseases, but also a clear need for core genetic competence has arisen in nearly every medical speciality. What is more, as genetic testing and genome sequencing are becoming cheaper and more readily available, the numbers of individuals and families with genetic disorders are increasing, while their expectations for their doctors are rising. Therefore, in order to ensure efficient patient-centred care and prompt prevention of avoidable mortality and morbidity, it is important that the new generation of doctors recognise the crucial role of genetics and genomics in their training and are prepared for it to become the central subject during the time of their clinical practice.

References

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11. Genetics in Primary Care, 2013. NHS NGEDC. Available at: http://geneticseducation.nhs.uk/genetics-primary-care
Community Based Genetics Elective, Vancouver BC

Matthew Pendleton, University of Dundee

I took part in a four week elective at the Vancouver Island Genetics program based in Victoria, Canada. The department is located in a general hospital just north of Victoria, which is the capital of British Columbia (BC). There are four Clinical Geneticists sharing the responsibility of clinics, with clinical interests including Rett Syndrome and Long QT Syndrome in the First Nations population. The team is completed by four genetic counsellors managing the majority of pre-natal counselling and two clerical staff.

Vancouver Island is home to almost 800,000 people, with Victoria situated in the south-east of the island serving as its secondary care centre. This presents geographical challenges for patients and clinicians in delivering care, a solution for which has been the use of telehealth. Despite not being an ideal form of communication it has proved invaluable in reaching small communities often isolated up-island.

This was my first experience of clinical genetics in action and I was fortunate to see a variety of conditions during my stay. I met adults referred to find answers, such as a gentleman with suspected CADASIL. The majority of the patients I observed were younger children referred for investigation and counselling for Autism Spectrum Disorders (ASD) including several children with Rett Syndrome. Dr Patrick Macleod, one of my supervisors has a particular interest in Rett Syndrome, playing a key role in establishing patient groups in Canada. The condition is thought to be on the most severe end of ASD, characterised by developmental regression in girls and stereotyped hand movements. Meeting families at different stages of the condition, all with such varied challenges, was very humbling and truly fascinating. Patient groups and social media have transformed the available support and information available to families new to the condition. This is particularly poignant in a region where some patients drive for over three hours for an appointment.

During my time with the department I also had the opportunity to assist with any urgent referrals, including a neonate with possible surfactant deficiency. This particular case allowed me to get to appreciate the practical aspects of investigating a possible genetic condition. For example, given that the tests were not offered within the state, funding had to be approved by the medical services provider in order to sanction public funding. The challenge of relating a differential diagnosis to an immediate clinical need that can be altered with a result was new to me. Whilst there are similarities that can be drawn in daily practice, the very real prospect of being refused treatment due to costs is something that medical students within the NHS are not accustomed to.

The experience of community based genetics in Canada is something that I have greatly benefited from. Given this is my first real exposure to genetics as an undergraduate it has opened my eyes to its complexity and future possibilities. This was a successful elective and a great experience, and as a result of this placement I am now looking at career options in the specialty.

Elective report

Shanya Sivakumaran, Edinburgh University

During my elective, I spent time with the clinical genetics teams at the Children's Hospital at Westmead, Sydney and at the National Hospital of Sri Lanka. I became interested in genetics during my intercalated degree, and have been able to attend a few clinics at the clinical genetics department in Edinburgh, which I found fascinating. I therefore thought that my elective period was a great opportunity to gain more exposure to the specialty.

My elective gave me an experience of the range of genetic conditions, as well as the contrast of genetic medicine in two very different environments, with different caseloads and cultures.

In Sydney, the mainstay of the clinical work was outpatient based, and the clinics I attended (neurogenetics, connective tissue disorders (including skeletal dysplasias), and prenatal, as well as general genetics clinics) gave me a taste of the wide range of conditions seen by geneticists. I also became familiar with common consultations such as neurofibromatosis, and discussion of recurrence risks of autistic spectrum disorder.

As well as attending clinics, I observed initial consuls of dysmorphic neonates in the neonatal unit, and the use of databases in order to try and establish a diagnosis. The department worked in a similar way to Edinburgh, with interesting weekly meetings in which clinicians shared photographs of cases they had seen during the week.

The Human Genetics Unit in Colombo is the only genetics unit in Sri Lanka. Whereas in the UK and Australia, many genetic conditions are diagnosed within other specialties, in Colombo, everyone requiring a genetic test is seen in this unit.
How rigorous is counselling for genetic testing? An audit performed during an elective in New Zealand

Emma Godfrey, University of Birmingham

BACKGROUND

Chromosomal microarray testing (CMA) is used routinely to aid genetic diagnosis for a wide range of conditions. Results can be ambiguous, generate uncertainty and raise ethical issues. CMA testing therefore requires clear patient information sheets and in-depth pre-test discussion for informed consent; results should be fed back in a timely manner and genetics referral made as appropriate.

Methods: Medical records were examined for children who had CMA requested by the Auckland Developmental Paediatric team in 2011 (n=28). Data abstracted were: demographics; receipt of written information about CMA; documentation of counselling (test discussion, possible results, DNA storage); written consent; the result, and documentation of when/how conveyed to parents; whether offered a genetic referral.

Results: Pre-test discussion was documented in 14/28, potential outcomes in 4/28 and DNA storage in 3/28. Eight received information leaflets and one gave signed consent. All three with abnormal results and 4/5 with variants of unknown significance (VOUS) were offered clinical genetics referral; 8/20 families with normal results were written to. Two with abnormal results were told their results in clinic and one was written to. VOUS were either communicated face-to-face (1), over the phone (2), by voicemail (1) or by letter (1).

Conclusion: This audit demonstrated problems either undertaking the necessary practices, and/or recording that they had been undertaken, highlighting the need for guidelines and training from the point of test introduction to improve clinical practice.

ABSTRACT

Background: Chromosomal microarray testing (CMA) is used routinely to aid genetic diagnosis for a wide range of conditions. Results can be ambiguous, generate uncertainty and raise ethical issues. CMA testing therefore requires clear patient information sheets and in-depth pre-test discussion for informed consent; results should be fed back in a timely manner and genetics referral made as appropriate.

Objective: To audit clinical practice against the gold standard of 100% documentation of the above.

Methods: Medical records were examined for children who had CMA requested by the Auckland Developmental Paediatric team in 2011 (n=28). Data abstracted were: demographics; receipt of written information about CMA; documentation of counselling (test discussion, possible results, DNA storage); written consent; the result, and documentation of when/how conveyed to parents; whether offered a genetic referral.

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Conclusion: This audit demonstrated problems either undertaking the necessary practices, and/or recording that they had been undertaken, highlighting the need for guidelines and training from the point of test introduction to improve clinical practice.
In order to improve the experience of families of a child having CMA, the audit was undertaken as the team were aware of differing practices between doctors, and of possible shortcomings in the provision of service in this area. At the time of the audit, no guidelines about CMA were available or in use in the unit. It aimed to identify areas needing improvement and to assist guideline development in order to improve the experience of families of a child having CMA.

The audit included all children for whom CMA was ordered by Auckland Starship Children’s Health Developmental Paediatric Team from 1 January 2011 to 31 December 2011. Patients were identified through return of laboratory results, checked with the laboratory to ensure all were included. Next all their computerised medical records were examined, extracting data listed in Figure 2.

Results were compared against constructed standards, developed primarily by literature searching through PubMed using the search terms ‘developmental paediatrics’, ‘microarray’, ‘counselling’ and ‘pre-test’ or ‘post-test’, and through conversations with professionals.

To check the quality of the results raw data was examined for outliers, notes were reviewed by a consultant if there were queries, data was compared against an initial less stringent preliminary work up by administrative staff (where any discrepancies were checked) and four patients were selected at random to be checked by an independent consultant.

Figure 1: Possible outcomes and their significance that should be explained:

- **Normal** – 65-70%: does not mean no genetic cause/ that their child is ‘normal’
- **VOUS** – 10-20%: further subdivided in to likely, uncertain and likely
- **Abnormal** – 5-20%: specific causal mutation identified
- **Incidental findings** <1%
- **Family relationships**: non-paternity, parental consanguinity, incest

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The audit showed clinical practice varied greatly

Results:
29 children had a CMA in 2011, of which one was excluded as they were on intensive care while tested. 22/28 were male, with a median age of 5 years 8 months (range 11 months-4 years 7 months). 10 were Asian, eight European, five Maori, four Pacifica and one other. Four tests were ordered by Senior House Officers and 24 by developmental paediatric consultants.

Findings for the different elements of the standard are shown below.

Pre-test: All patients should have appropriate pre-test counselling in order to achieve informed consent, including discussion of: potential test: Documented: 14/28 (50%)

Outcomes: Documented: 4/28 (14%)

Storage of DNA: Documented 3/28 (11%)

A plan should be made on how results will be communicated, including normal results and those of uncertain significance: None documented

All patients should be given a CMA Parent Information sheet: Documented 8/28 (29%)

All should sign a consent form agreeing to the procedure: Done 1/28 (4%)

Test results: Three had abnormal results (Smith-Magenis Syndrome, microduplication of 7q 11.23, Phelan-McDermid syndrome) and five had VOUS

Overall 16/28 (57%) were informed of their results

Patients should be informed of their abnormal test result face to face, within 4 weeks of the result becoming available: 2/3 patients were informed at clinic and one was written to, after a median of 36 days (7-42). It took longer to write to the patient.

Patients should be informed of a VOUS within 4 weeks of the results becoming available, how this is done being decided in advance with the patient: One family was informed face to face, three by phone (one of whom was left a message) and one was written to, which took a median of 25 days (2-246 days)

Patients should be informed of normal results in writing within 4 weeks of the results becoming available: 8/20 patients with normal results were written to. The median time was 6 days (2-81 days) for one a date was unavailable.

A genetics referral should be offered to all families where there was an abnormal or VOUS result within 4 weeks of the result becoming available: All three with abnormal results and 4/5 with VOUS were offered a clinical genetics referral (the patient that was not referred was seen by a consultant paediatrician in clinic).

Discussion

The audit showed clinical practice varied greatly, with management of no family meeting all the recommended guidelines. Indeed these audit findings are cause for concern, with the only standard achieved >50% of the time being genetics referral. However, what this audit cannot show is whether this reflects poor documentation of discussion or a lack of appropriate clinical practice. While doctors are notoriously poor at documenting what they do11, it is very important to ensure appropriate documentation in patient notes as this not only improves patient care, but provides evidence in case of any future dispute or investigation18.

CMA was introduced in Auckland in 2010, meaning that this audit reflects a time where clinicians were becoming familiar with this relatively new test. Although the Starship team are now confident in using CMA, when it was introduced many said they were uncertain. Several articles found a worldwide need for better training of those ordering CMA as many felt unequipped to counsel and interpret results6,9,12. This is a particular issue in many settings as the capacity of the medical genetics workforce is often insufficient to meet demand6,5, in Auckland waiting lists are up to six months19.

Currently there are no gold standards published from any professional body. Several papers have stressed the need for formal updated guidelines6,9,12 to improve clinical practice6; current American Academy of Pediatrics recommendations14 for genetic testing predate the use of CMA. For my audit standards were developed using the current literature (primarily New Zealand or Australian, supported by European and American articles) and through discussions with genetic and developmental paediatric specialists in New Zealand and England. Discussion after my audit agreed that the gold standards developed were appropriate for future use, with the possible exception of written consent. Some argued that CMA does not cause ‘significant adverse effects on the consumer’ and therefore written consent may be unnecessary under Health and Disability Commission Code, and could detract from what the clinical encounter is really about16. Contrastingly, Cohen et al found that patients found it served legally to document consent and as source of information for the family9. Moreover, current practice at Auckland’s genetics department uses written consent forms as common practice due to the ethical aspects of genetic testing19.
Therefore the plan is to use written consent forms at the clinician's discretion.

The notes suggest that informed consent was not obtained for CMA or DNA storage in the majority. For a patient/family to be able to give informed consent they need to have been given information about the procedure, its purpose, other testing option, and possible outcomes15. Under Rights 6(2) and 7(1) of the New Zealand Health and Disability Commission Code it is a legal requirement to obtain informed consent before any procedures/investigations16. Informed consent through pre-test counselling also helps patients understand the outcomes and reduce anxiety.

**Figure 4:** The New Zealand Health and Disability Commission Code on informed consent16

Right 6(2): Before making a choice or giving consent, every consumer has the right to the information that a reasonable consumer, in that consumer’s circumstances, needs to make an informed choice or give informed consent

Right 7(1): Services may be provided to a consumer only if that consumer makes an informed choice and give informed consent, unless there are reasonable grounds for believing that the consumer is not competent

Rights 7(9) and (10) of the Health and Disability Commission Code govern the legality of DNA storage16. It especially needs to be addressed in New Zealand, in light of the Greenlane scandal20 and in respect for Maori culture21. The tangata whenua (people of the land) view DNA and genes as tanonga (property/possessions); in 1840 Chiefs signed the Treaty of Waitangi with the Crown to have ‘undisputed control over their land, their villages and their possessions’. Extra counselling and consent may be required as many Maori people do not support patenting of genes or sending DNA off-shore for testing and storage of DNA as it is their property21.

**Figure 5:** the Health and Disability Commission Code on DNA storage16

Right 7 (9): Every consumer has the right to make a decision about the return or disposal of any body parts or bodily substances removed or obtained in the course of a health care procedure

Right 7 (10): Any body parts or bodily substances removed or obtained in the course of a health care procedure may be stored, preserved, or utilised only with the informed consent of the user.

To improve families’ experiences and ensure they receive appropriate counselling a checklist form should be developed documenting the steps involved in pre test discussion (figure 6), which clinicians can refer to.

**Figure 6:** Checklist for pre-test meeting

- Discussion of what the test involves
- Discussion potential outcomes
- If the family are happy to go ahead with the test
- Discussion and consent for DNA storage
- Information leaflet given
- Consent form signed

This audit has identified several aspects that can be implemented to improve the experience of families undergoing genetic testing. Furthermore, it has highlighted the need to proactively develop guidelines and implement clinical education when new tests are introduced. While this can be applied to any field, with the rapidly expanding field of clinical genetics and the introduction of exome sequencing it is even more imperative as this highly sensitive test will detect ~400 novel sequencing variants even in healthy individuals, thus discovering more VOUS3. Moreover exome sequencing is more likely to uncover incidental findings which are present in ~1% of the population8.

No previous audits have been done on the process of CMA; this audit highlights the importance of assessing clinical standards in conducting genetic testing as there is room for significant improvements to be put in place.

A re-audit should be done in 18 months time to assess the impact of the changes suggested.

Acknowledgements:

I would like to express my very great appreciation to Dr Philipa Clark, developmental paediatrician Auckland New Zealand, for her support and advice. I would also like to thank; the Clinical Genetics Society, the Stuart Green Memorial Trust, and the Institute of Medical Ethics for their generous contributions.

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International Scholarships 2012

Dr Artyom Gaspayyan
Yerevan, Armenia

It was an honour for me to have that chance. I’m very grateful for all the knowledge I have got due to the scholarship as it helps me much in my job. All the practice and knowledge I have got is very useful for me and this is most valuable. That is why I’d like to obtain more knowledge and practice in order to help people and make their life better.

Dr Michael Urban
Stellenbosch, South Africa

It gives me a warm feeling to hear from you and CGS again! My time in the UK was very valuable and all the more so because I am at a small genetic centre (and needed the extra input!), and had not done Clinical Genetics outside of South Africa (SA) previously.

I had a great 2 weeks in Newcastle, both at the conference and the clinical attachment afterward. In particular, Alex Henderson was an organised and warm host, who put me in touch with as many people as I could cope with and then a few extra! I have had subsequent useful communication with the Centre for Life: Alex Henderson and Paul Brennan gave me advice regarding genetic testing policy issues; Brian Wilson gave info regarding registrar training options; we have also since sent BRCA sequencing samples to the Newgene lab in Newcastle.

Outcomes thus far (learning and/or practical):

- I attended an afternoon of the Cancer Genetics group and subsequently a Cancer Genetics Clinic with Fiona Douglas which was eye-opening. This gave me some practical ideas about developing cancer genetics locally. I then sent our genetic counselor to the Southampton Cancer Genetics course. We have since improved our cancer genetic counseling – still mainly breast cancer but have added colon cancer and working on others. We have improved our access to cancer genetic testing (mostly not on-site), and have reasonable access to BRCA testing and to Lynch immunohistochemistry and genetics.
- I spoke to Judy Rankin about the NORGAS Birth Defects Registry because birth defects surveillance is very limited in SA. Again this gave me some practical ideas about how to get started in a simple way. I now have a registrar doing her research project on surveillance for Neural Tube Defects.
- I got a reasonable sense of the registrar teaching system in Newcastle, which has helped me improve registrar training locally. For example, I am trying to improve training in cardiogenetics – this was low on my radar, but I have pushed it up the priority list and found someone in internal medicine with knowledge and interest (it is an interest area at Stellenbosch University).
- After seeing the UK Dysmorphology meeting format, we have tried to emulate it in our own small way at our twice yearly national Dysmorphology Teleconference.
- We are improving our access to testing for rare disorders through a link between a local private lab and the UKGTN. This will improve the deal that people with rare diseases get (currently poor – very limited access to testing, minimal access to therapies such as enzyme replacement).
- I am working actively on improving our approach to clinical bioinformatics. Struggling at present, but am looking at one of us attending a course at the Sanger Centre which I found out about while at Newcastle.
- I had useful discussions with Laura Yates from UK teratology information service, but haven’t had time to translate this into a practical outcome yet.

We battle with many issues – especially related to genetic diagnostic testing (our set-up is limited). In addition we have major problems with Fetal Alcohol Syndrome – this is a public health issue in our province and we do our best to provide a diagnostic service and involve ourselves in FAS research. This said, a brief immersion in a different system was ideal for flagging important clinical, lab and public health issues that I have tried to address. I hope for ongoing support from CGS colleagues.

All the best to the next international fellows, and thanks again to CGS! Please feel free to ask for any further input, or to make suggestions.
Externship report
Dr Vinod Cherian Varghese, Institute of Medical Genetics, Cardiff

I was very excited when Professor Daniela Pilz mentioned an externship opportunity at the Centre for Human Genetics (CHG), Bangalore, India. The Clinical Genetics Society were initiating a programme, where Genetics trainees in the UK could spend time at a high volume centre thereby gaining valuable experience in a short period of time. Professor Pilz and Dr Peter Turnpenny had been in contact with Dr Meenakshi Bhat at CHG, who kindly agreed to take me on as an observer for four weeks. I was awarded a travel grant from CGS, which was very useful and I am grateful for the same. I am also thankful to my training programme director, Dr Alex Murray and educational supervisor, Dr Annie Procter for their support while organising this externship.

Centre for Human Genetics (CHG), Bangalore is one of the premier Genetics institutes in India, led by Professor Sharat Chandra, who is the Director of the Institute. Dr Meenakshi Bhat leads the Clinical Genetics team. The fact that Dr Bhat used to be a Consultant in Guy’s & St Thomas’ Hospital meant that I would be training under someone who was aware of the training requirements in the UK. My externship at CHG started on 10 September 2013. CHG is located within the heart of ‘Electronics City’ in south Bangalore, the Silicon Valley of India. I reached the Centre a few days prior to the date of commencement of the programme. Mrs Jayaraman, the coordinator, and other staff at the centre were very helpful. They had arranged for an accommodation close to CHG during the period of my stay in Bangalore. I was also given a brief overview of Dr Bhat’s clinics, which included two regular clinics per week – Tuesdays at Bangalore Fetal Medicine Centre (BFMC), a tertiary fetal medicine centre, and Wednesdays at Indira Gandhi Institute of Child Health (IGICH), which is the largest children’s hospital in Bangalore. Although both of these clinics were located some distance from CHG, the regular city bus services ensured that travel was comfortable.

Paediatric Dysmorphology
We saw about 15 children a day in each of these clinics, which was quite different from the numbers in Cardiff (about 6-8 patients per week). One of the very first families I saw at the clinic were two siblings severely affected with Xeroderma Pigmentosa. Unfortunately, the family hails from a rural part of the state and the children never had a formal diagnosis made prior to this and no preventive measures were taken to prevent deterioration. The other cases I saw that day included a child with Hurler Syndrome, a child with suspected Rett Syndrome and another with Griscelli Syndrome. Once back at the CHG, it was very interesting to look at the hair sample of the child with Griscelli Syndrome, which showed the classic picture of melanin clumps. Over the next four weeks I was able to see some rare conditions including Bruck Syndrome, Ellis Van Creveld Syndrome, Cutis Laxa and a mother-son pair with Coffin-Lowry Syndrome. I was also able to see relatively common conditions like Duchenne Muscular Dystrophy, Stickler Syndrome and ectodermal dysplasia.

Another child had a combination of thalassaemia intermedia and Blepharophimosis Ptosis Epicanthus Inversus. Dr Bhat also organized Noonan and Prader-Willi Syndrome clinics. The spectrum of problems seen in these children offered a significant learning experience. There were quite a few children with inborn errors of metabolism. Apart from children with mucopolysaccharidoses and glycogen storage disorders, I saw an infant diagnosed with maple syrup urine disease. Although the treatment for many
“Dr Bhat is an astute dysmorphologist and an excellent teacher”

Centre for Human Genetics, Bangalore

of these metabolic conditions are beyond the reach of the rural population, it was really heartening to see Dr Bhat liaising with various agencies to provide enzyme replacement and special dietary formula for several of her patients. Many genetic tests were undertaken in the accredited Cytogenetics and Molecular Genetics laboratories within CHG, while others were sent to other laboratories within and outside India.

**Prenatal Genetics**

Dr Bhat explained that there was an increase in prenatal referrals over the years due to an increasing awareness among doctors, who now referred couples with a family history of a genetic condition. The cases I saw included the common referrals like family history of a child with congenital anomalies or chromosomal rearrangements. There is an increased incidence of thalassaemia across India and this was one of the recurring themes in the clinic. The couples generally opted for prenatal testing if the genetic cause was identified in the family. In many cases, there was no definite diagnosis made. When appropriate, these patients were offered detailed antenatal scans. I got the impression that couples had a lower threshold for termination if any anomalies were detected on scans. This might be due to inadequate support systems for children with disability compared to the Western countries.

**Conclusion**

I would recommend any Clinical Genetics trainee looking for a ‘crash course’ in paediatric dysmorphology, to spend a short period of time at CHG, under the guidance of Dr Bhat, who is an astute dysmorphologist and an excellent teacher. I am extremely grateful to Dr Bhat and all the others at CHG who made my experience truly memorable!

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**Letter from the President: Coping with scoping**

Jill Clayton-Smith, Manchester

I seem to have been doing a lot of ‘scoping’ recently. Many official bodies including NHS England, NIHR and NICE have become quite keen on scoping, so much so that when I searched my inbox to check for communications on ‘scoping’ it came up with a huge selection of e-mails across various topics. Of course, there was some evidence of less serious scoping activity - checking out places to go on holiday and retail opportunities, but quite a lot of my recent scoping has been real important stuff.

So I checked out the definition of scoping. To scope: to assess or investigate something. To look at carefully or to scan. Getting the information required to start a project, and identifying the features the product would have in order to meet its stakeholders’ requirements.

Scoping is a serious subject - I found that the European Union have previously published a 35 page document with a framework for ‘how to scope’ and a special scoping checklist. Whilst many pages of this make for a rather dull read, the overall principles of scoping which they set out at the beginning are in fact very relevant for most of the scoping exercises the genetics community have been involved in recently and worth noting if you plan to organise a scoping event yourself. To scope effectively you need to:

1. provide enough information about the project for consultees to understand what is proposed and identify potential issues
2. make clear to participants that the scoping process is about hearing and understanding their views not about selling the project
3. provide sufficient time for consultees to respond to requests for views and information
"sometimes you get that little frisson of self satisfaction"

4. reassure consultees that any views which they express at the scoping stage will not preclude them from making further comments and possibly objecting at a later stage
5. ensure that the views expressed are taken into account, and are seen to be taken into account and that an explanation is provided if recommendations are not followed.

I have realised that some of my scoping experiences have not been ideal. In a scoping exercise on using Next Generation Sequencing as a frontline diagnostic tool it was I who had the challenge of explaining in detail to the scopers what NGS was, not the other way round. Going through its advantages and disadvantages and how it differed from current testing left me well and truly scoped out. The Genomics England 100,000 genome project has involved a lot of scoping, but although they did indeed organise stakeholder participation they could perhaps have done a little better on some of the points above. One of my best scoping experiences was at a recent national scoping event for the Specialised Services Strategy, organised by NHS England and the Specialised Healthcare Alliance. Though the information given was in bite-sized chunks, it covered topics like quality and safety, innovation, integration, money and accountability in what was mostly understandable language, and the scopers had been selected to cover a broad range of stakeholders, from local councillors, industry reps, and clinicians to some very inspirational and well-informed patients who taught everyone a thing or two.

Some scopers make good use of IT nowadays. Everyone might be given a little pushbutton device for communal voting, the results of which you see instantaneously on the screen before you, or the twitterati might even be encouraged to tweet throughout the proceedings. Of course, at most scoping events there are the inevitable flip charts. (Why am I always the one on my table who gives in and volunteers to be the scribe.....). At the end our sheets of paper are collected and taken away – sadly some of what we thought were pearls of wisdom seem to go with them, never to see the light of day again (see point 5 above). However, sometimes you get that little frisson of self satisfaction when the workshop report arrives and you see there in black and white the point you eloquently put forward.

So yes, I am getting into scoping. A good scope provides you with new knowledge and really encourages you to think around a subject. It provides an opportunity to put forward your point of view and that of the people you represent and what’s more, you can meet some great people. There might even be lunch.

Scoping is in progress as we speak. The trainees in clinical genetics are being scoped to ask about their previous background, research experience and their aspirations, knowledge which we are keen to capture for workforce planning in particular. The RCP manpower survey is carrying out scoping along similar lines and I would encourage you to engage (though my response to the question on when I plan to retire seems to fluctuate widely depending on how rewarding or otherwise my job has been that week and is perhaps not too reliable). Scoping is definitely the new type of awayday. Better not get too hooked on it, though. Wikipedia says there is something called ‘scope creep’. I definitely don’t want a dose of that!

The joint Clinical Genetics Society Conference is fast approaching (17-18 March 2014). The destination is Leiden in the Netherlands and hopefully we will have a considerable trainee representation. However, an international conference highlights an increasing problem for trainees in an unbanded specialty with ever-reducing study leave budget. This inevitably restricts attendance at conferences and courses unless trainees self-fund. I would like to remind you that the CGS can support you with travel awards to those attending international conferences.

The changes in NHS commissioning are an important current topic. Clinical Reference Groups (CRGs) are the reference source for NHS England for the establishment and maintenance of specialised services. The groups include clinicians, support groups and patients. There are 74 CRGs (which include Medical Genetics) divided into 5 main care programmes. Although the groups are now established, they are taking registration for stakeholders who can have varying degrees of participation, from receiving information on CRG events to involvement in the development of services. This could be an opportunity for Genetics to formally collaborate with other specialties in establishing joint specialised services, it will be interesting to see how the groups progress.

As you are aware from the previous newsletter, the CGS has entered the world of social networking with twitter and Facebook accounts. At present there has not been much interaction coming back from the membership either via the website or on the twitter or Facebook pages. Facebook is a closed account and you will have to request membership.
Social media update

Shane McKee, Belfast

Both will improve information sharing, so please post any good links, comments and thoughts. The links can be found via @clingenSOC on twitter and www.facebook.com/groups/clingenSOC.

There have been no changes made to training over the last few months. The third sitting of the knowledge-based assessment exit exam will be in March.

If you have any training issues that you wish to be expressed at a national level, particularly if you have any suggestions of how the society can help support and promote training, please contact myself (Emily Craft @uhl-tr.nhs.uk) or Hannah Titheradge (htitheradge@doctors.org.uk). If you have training issues please contact the SAC representatives, Clare Searle and Emma Burkitt Wright.

Engagement and communication have been key to the success of CGS over the years, enabling discussion, research, collaboration, friendship and support among our members. This in turn has enabled our specialty to develop and to improve services for our patients. As part of our overall wish to move this forward, CGS has embraced the Twitter and Facebook revolutions, and while we’re not exactly hitting Lady GaGa levels, there is a small frisson of activity, indicating that this is being well received.

The BSGM Conference in Liverpool was a useful testing ground for the Twitter engagement strategy; we did have a few people posting using the hashtag #BSGM2013, but not as many as I had hoped (to be perfectly honest), and nowhere close to the deluge from ASHG in Boston with #ASHG2013. Nevertheless, it’s a start, and hopefully #CGS2014 in Leiden will mark the tipping point.

We have 26 members of the Facebook group and 87 followers on Twitter – I think we can do better than this, but the key is for it to actually deliver value to the membership. So if you’re not connected already, please toddle over and contribute your research updates, interesting links, thoughts on recent developments and general chit-chat.

• Join us on Facebook: www.facebook.com/groups/clingenSOC
• Follow CGS on Twitter: @clingenSOC
• Keep an eye on the CGS website: www.clingenSOC.org
• Join the CGS LinkedIn group – e-mail me on shane.mckee@belfasttrust.hscni.net if you’d like to join

We know that most NHS trusts block access to Facebook and Twitter, but this is less of an issue now for those of us with smartphones. We’re also entirely realistic that these modes of communication are not to everyone’s taste, however, we do want to offer a few alternatives for members. If you have any bright ideas, please contact the CGS Secretary, and/or post them directly to the Facebook and Twitter feeds. Courses, research recruitment calls, conferences, funding announcements – all are welcome. Hope to see you on-line soon!
Preimplantation genetic diagnosis at the UCL Centre under the new NHS England funding

Joy Delhanty, University College London.

From April to early October we have carried out pre-implantation genetic diagnosis (PGD) for 20 patients under the new NHS England funding scheme. Thirteen became clinically pregnant and 12 couples now have an ongoing pregnancy. The average age of the mother was 30.7 years. For four couples there were no unaffected embryos to transfer. So for the 16 couples with transferable embryos the pregnancy rate overall was 81%.

NHS England funding is available for couples that meet the criteria: no unaffected children from either partner; the woman’s age under 40 at the time of treatment and her BMI under 30.

Apart from offering PGD for all kinds of chromosomal rearrangements that are diagnosed using array CGH or FISH as appropriate, we have carried out the diagnosis for multiple single gene disorders. De novo cases and those with no available relatives are accepted.
Welcome to the first Cancer Genetics Group Newsletter of 2014. In this edition we have an update from CGG Chair, Fiona Laloo summarising all that’s contemporary in clinical cancer genetics. From James Whitworth we have a summary of the packed agenda at our winter meeting, Ian Frayling has a great overview on important developments with Lynch syndrome and for the latest in our series of 10 minute interviews we are greatly honoured to have Professor Bruce Ponder reflecting on his long and illustrious career in cancer genetics.

Fiona Laloo rounds-up a busier than usual year for clinical cancer genetics. Updated NICE Guidelines for hereditary breast cancer care bring new challenges and opportunities to genetics and breast care services. Ambitious new recommendations on chemoprevention, lowered mutation testing thresholds and extended breast surveillance protocols raise practical, logistical and resource issues. But perhaps our biggest recent challenge was a massive increase in breast cancer referrals. This was almost exclusively attributed to the story of film actress Angelina Jolie’s decision to undergo risk-reducing mastectomy following a genetic test which revealed she carries a BRCA1 mutation. The so called ‘Angelina effect’ was sustained for several months, having a wide ranging impact on genetics services and highlighting the influence of celebrity figures on health understanding, attitudes and behaviour.

After a well attended CGG winter conference at the end of November, James Whitworth, Specialist Registrar at Birmingham Women’s Hospital presents his thoughts on an excellent meeting. This year we had a new venue, the Chester Beatty Laboratories at the Institute of Cancer Research in Chelsea. James updates us on all the major cancer genetics studies, plus an overview of some newer projects and a timely review of breast cancer chemoprevention studies presented by Professor Trevor Powles. He's been closely involved in the trials for many years.

One thing the Steering Group has noticed is the relatively low attendance of Genetic Counsellors at the winter meeting. We strongly encourage and would warmly welcome more GCs to the meeting, it has much to offer!

For this edition of the Newsletter our main clinical oriented article is from Ian Frayling, Consultant in Genetic Pathology at University Hospital Wales. Widely acknowledged as an authority in colorectal cancer genetics, Ian gives an update on testing for Lynch syndrome (LS) including the latest from the Mallorca Group (InSiGHT in Europe) on interpreting MMR gene mutations. Ian’s commentaries are timely, being the subject of major articles in Gut (clinical management of LS) and Nature Genetics (mutation interpretation), the latter having attracted considerable media attention just before Christmas. A growing recognition of the limited utility of family history assessments for identifying people at risk of LS and inadequacies of the Bethesda criteria for tumour testing was the impetus behind the Mallorca group’s ambition to develop new clinical management guidelines. Ian captures the essence of their prodigious efforts. Systematic testing of LS-cancers has been adopted in several countries now, including the Netherlands and USA. In the UK it was suggested some years ago that the NHS Health Technology Assessment scheme ought to look into this too. Now Ian draws our attention to a much anticipated HTA report (over 600 pages). The bottom line is that it would to be cost-effective for the population if all colorectal cancers up to age 70 are tested for evidence of LS, even isolated cases. Ian summaries the six year programme undertaken by InSiGHT to investigate MMR gene mutation interpretation, an increasingly important topic given the reducing cost and increasing capacity to detect potentially high risk predisposing mutations. Essentially, they have successfully classified all of the 2000 plus mutations on the InSiGHT database, with some important findings concerning (class 3) mutations with potentially reduced pathogenicity/penetrance. See the Nature Genetics article for the complete picture, which is free to access.

We finish with the latest in our series of 10 minute interviews. For this edition we are very proud to announce that Professor Sir Bruce Ponder, Director of the CRUK Cambridge Research Institute, has generously given his time to share with us some thoughts on his illustrious career. He offers a fascinating tour through a life devoted to cancer genetics, signposted by some of the key events in genetic medicine, including his discovery of the RET gene in multiple endocrine neoplasia-2 (MEN2) and in developing the first familial cancer clinics in the 1980s. In more recent times Professor Ponder’s focus has primarily been on research, but his contribution through four decades to the clinic and the laboratory has few revivals, and he’s still going strong. Read with interest!

Andrew Cuthbert, Editor
A message from The Chair

Fiona Laloo, Chair Cancer Genetics Group
Consultant Clinical Geneticist and Lead Clinician, Clinical Genetics Service, Manchester
Centre for Genomic Medicine, Manchester

I am delighted to say that we have just had an excellent winter meeting in London and we are now looking forward to the joint meeting with the Clinical Genetics Society and our Dutch colleagues in Leiden in March 2014.

This past 12 months has been extremely busy for everyone with a number of changes within cancer genetics including the increasing emphasis on mainstreaming cancer genetics and the publication of updated NICE guidelines on familial breast cancer. Along with this, there appears to have been a national increase in referrals following Angelina Jolie’s revelation about her BRCA1 status and risk reducing mastectomy.

The mainstreaming agenda is moving forwards. The meeting held at ICR in the summer was both enlightening and exciting. It was very useful to have all the leads of the cancer genetic services in the same room and to realise that we are addressing similar issues in our services. I understand that further meetings are planned which is to be welcomed.

The NICE guidelines relating to the use of Tamoxifen and Raloxifene have raised some specific challenges for clinical services and it was therefore timely that Professor Trevor Powles gave an overview of chemoprevention studies. It was also reassuring that he felt that the NICE guideline was ambitious in its demands of clinical genetic services. CGG has developed information leaflets for patients regarding chemoprevention and these will be available on the CGG website by the end of January.

The requirements for cancer genetics expertise within regional genetic centres and input into general areas of medicine are increasing and it was with this in mind that CGG (along with CGS) has embarked on a survey of trainees within clinical genetics. The aim of this is to establish the expectations and areas of subspecialty interest within the trainee body and if necessary tailor some of the recruitment processes for our specialty. I hope that we will have some data to report back to CGG at the meeting in Leiden.

The winter meeting is always extremely useful as a reminder of the breadth and diversity of research within cancer genetics in the UK and this meeting introduced some potential new studies. There will be a synopsis of these studies on the website.

Finally, I wish you all the best for 2014.
The winter edition of the Cancer Genetics Group meeting took delegates to the Chester Beatty Laboratories at the Institute of Cancer Research in November for its ever stimulating summary and update. As previously, an emphasis on both new and long running research projects was complemented by broader insight and discussion with a particular focus on pharmacological management on this occasion. Many of the studies now have impressively large numbers of recruits and thanks were frequently expressed by researchers towards the centres and research networks that have made this possible.

Many of the studies presented are well established and in fact are coming to an end in some cases. A number of them address specific clinical questions relating to individuals with cancer susceptibility syndromes frequently seen as part of clinical genetics practice. The EMBRACE study has used its large cohort of BRCA1 and BRCA2 mutation carriers to characterise phenotypes, identify modifier loci and contribute to international collaborations. One current focus is cancer risk estimates based on prospective analysis to avoid biases resulting from retrospective study and preliminary data was presented in this regard.

The question of prostate cancer screening in carriers of mutations in these genes has been addressed by the IMPACT study, which will close to recruitment in January. IMPACT aims to assess screening in other prostate cancer germline risk variants as they are discovered and a new series of Lynch syndrome cases is being recruited to this end.

Screening issues relating to those with a family history of breast cancer and carrying a TP53 mutation form the basis of the FH01/FH02 and SIGNIFY studies respectively. FH01 (screening in women aged 40-49) has now concluded and reports a cost effective likely mortality reduction in screened individuals. FH02 (age 35-39) is due to stop recruiting as of 2014. The SIGNIFY study has already begun performing full body MRI scans on TP53 mutation carriers. Incidental findings in the scans will be recorded and discussed in the context of the MRI technique used. Diffusion weighting has been utilised but not contrast to allow imaging without an attending medic. The possibility of a tumour pathological phenotype in germline TP53 mutation associated breast cancer is being investigated by the COPE study using various techniques including immunohistochemistry and tumour sequencing. Recruitment remains active via anonymised pathology report/discussion with the study team in Southampton.

An array of current projects, some established and some new, were presented whose focus is on disease-gene association via the utilisation of next generation sequencing techniques applied to cancer phenotypes suggestive of germline predisposition. Eligibility criteria for these studies are often broad to favour large series and a high throughput approach, frequently expanding beyond phenotypes traditionally associated with clinical genetics practise. The ICR studies BOCs (breast/ovarian cancer), FACT (childhood tumours), COG (overgrowth) and UKGTCS (testicular cancer) have established such series and more recent findings were discussed such as novel cancer predisposition genes associated with childhood cancer and new loci associated with testicular cancer. Interestingly, the latter study has a web/e-mail based self-recruitment mechanism using a web address that can be passed on by a clinician without taking consent at the time.

The familial gastric cancer study is identifying relevant genetic variants (in part via whole exome sequencing of CDH1 negative cases) and informing management guidelines for hereditary diffuse gastric cancer, which will be updated in March 2014. Two newer gene association projects were presented that aim to recruit individuals who have been diagnosed with multiple primary cancers. The multiple primary study in Cambridge will perform genetic analysis on blood and tumour samples and the GemCaS study at the ICR will analyse blood samples from a similar patient series. Patients can be recruited to both studies simultaneously.

It is exciting to consider the increasing developments in pharmacological management for genetic conditions and a significant section of the meeting was occupied by this area. Both the reported success and cost effectiveness of aspirin in Lynch syndrome are striking and an update of the CaPP3 dose inferiority trail was presented. This, in part, highlighted the additional organisational challenges of intervention based clinical trials perhaps not frequently encountered by researching geneticists.

The evidence regarding the use of another established group of drugs, namely oestrogen receptor modulators and aromatase inhibitors in breast cancer risk reduction was presented by Professor Trevor Powles (ICR). This was particularly
Developments with Lynch syndrome

Ian Frayling
Consultant in Genetic Pathology, Laboratory Director, All-Wales Medical Genetics Service, Institute of Medical Genetics, Cardiff

There are a number of ongoing developments in Lynch Syndrome (LS) which will be of interest to all, not just to those who specialisation is cancer genetics, let alone bowel cancer.

**Systematic testing of tumours to ascertain LS?**

The dawning recognition that family history has limited utility to identify those at risk of LS has stimulated work to address this. The European branch of InSiGHT (http://www.mallorca-group.eu/) has published both an update to their clinical guidelines for LS (which is free to access, with thanks to the CGG: Vasen, Hans FA, et al. "Revised guidelines for the clinical management of Lynch syndrome (HNPCC); recommendations by a group of European experts." Gut 62.6 (2013): 812-823.) and also a paper on how best to identify cases of LS (Vasen, H. F. A., et al. "Recommendations to improve identification of hereditary and familial colorectal cancer in Europe." *Familial cancer* 9.2 (2010): 109-115.).

The Bethesda criteria to select tumours suitable for testing for deficient mismatch repair - so a marker of LS - were published some time ago with a later revision, but it is accepted now that these have limited utility, being complicated and lacking sensitivity and specificity. If taken as read, application of the criteria would result in ~25% of all colorectal cancers being tested. As the LS phenotype associated with each individual gene (MSH2, MLH1, MSH6 and PMS2) becomes better defined, so it becomes clear that typical clinical thresholds for referral to family cancer clinics, and the performance of the Bethesda criteria in identifying cases of LS vary widely between the genes, and in particular MSH6 and PMS2 with lower penetrance and later onset are especially prone to under-ascertainment.

Some will be aware that Norway, Denmark, The Netherlands and the USA now have programs of systematic testing of LS-associated cancers. Some years ago the NHS Health Technology Assessment scheme was asked, by those of us who could see the way things were going, to look at the question of systematic testing of colorectal cancer for LS and subsequent cascade testing in relatives – would it be cost-effective? This brief (10/28/CB) was subsequently picked up by the NIHR-funded health economics unit at the University of Exeter, the Peninsula Technology Advisory Group (PenTAG), who engaged a number of experts, and we got on with the job. Now, nearly two years later, having determined first that no suitable analysis had already been performed, and then having designed a health economic model a 641 page report is in the offing, which will be available via http://www.nets.nihr.ac.uk/projects/hta/102801, thanks to the hard work of all concerned, including the PenTAG team.

All aspects of care and costs surrounding cancers, clinical genetics, laboratory testing, social care, training, psychological and other disbenefits, to name but a few, have been incorporated in the model. A number of different tumour testing strategies were looked at, but the upshot is that it would be cost-effective to test all colorectal cancers in the UK for evidence of LS using any of the current methods, and then if such evidence should be found then to recommend referral to cancer genetics services. Interestingly, it comes out as cost-effective to test even if the only LS case ascertained is the proband, although it does increase if relatives are found. We looked at different ages of cut-off, and

Overall then, an extensive update with insights into the past, present and future of clinical cancer genetics. The next meeting will be in Leiden, Netherlands on 17th and 18th March 2014.
testing would still be worthwhile up to age 70. Above this the yield of LS cases will drop off, and resources would probably be better allocated to test endometrial and other LS-associated tumours – something we want to look at in detail with an extension to the work. It is pleasing that some regions in England are now forging ahead with implementing this (allied to oncologists’ requests for MSI testing to help them decide on therapeutic options), and it would be of clear benefit if this could be monitored on a UK national basis so e.g. in service improvements and proof of efficacy could be determined and quantified.

Also on the horizon is the use of aspirin prophylaxis in LS. The CaPP3 trial is planned in order to determine the best dose of aspirin to use, it having already been established that aspirin would reduce cancer burden in LS, and by a considerable degree (http://www.capp3.org/). It is notable that, on the basis of Canadian safety data, annual colonoscopy for 100,000 gene carriers for 10 years would be expected to cause the death of 70 while halving the colon cancer rate, whereas regular aspirin would not be expected to cause any deaths and would more than halve the number of all LS-associated cancers. So, as and when aspirin prophylaxis is with us as an established treatment for LS, the cost-effectiveness of finding LS cases would become overwhelmingly positive.

Interpretation of MMR gene mutations
An increasingly thorny issue over the last decade is how we interpret the variants we now have, especially as it has become cheaper and quicker to find them. There are a number of leads one can take from clinical data, segregation and such like, plus in LS we have the lucky break of data from tumour tests. Also, there are various in vitro models, developed in the basic research setting, which can give clues to the pathogenicity of variants by looking at evolutionary conservation of amino acids, or predicting mRNA splicing abnormalities. However, the in vitro models in particular suffer from being general and in themselves not sufficiently predictive of pathogenicity that their outputs can be used in the clinic. InSIGHT therefore decided over six years ago to look at this whole issue of interpretation. We recognised that we had a large database of mutations, we could incorporate data from tumour and family analysis and more importantly it would be possible to incorporate unpublished data from clinical laboratories, which being accredited meant that their data would be of the highest quality. Also, if we could help address the issue then any model we came up with could be used by others working on other diseases and genes. So, a group of over 40 of us got together and started work. We really needed this many as between us we could cover all aspects of the work, from clinical application of the results, interpretation of tests, and even counselling.

We decided to use the 5 class system defined by Pion et al (Class 5 – Pathogenic, Class 4 – Likely pathogenic, Class 3 – Uncertain, Class 2 – Likely not pathogenic, and Class 1 – Not pathogenic), and that classes 1, 2, 4, and 5 would be clinically actionable. We also decided that while our ultimate target would be a completely objective probabilistic model based on Bayesian statistics to give probabilities of pathogenicity, we weren’t going to get there in one go, and to start with a more qualitative pragmatic approach would be needed where necessary.

With the fortune of a large database, we were able to use those variants classified unequivocally by other means first to determine which in vitro models best predict pathogenicity in MMR genes – just two of them as it turns out: PolyPhen2.1 and MAPP, used in combination, and then improve them by recalibration using the already defined variants. This allowed us to tackle the apparent missense mutations. We’re continuing to work on defining best models for splice-site mutations, so we are by no means finished. That will require a load of data from mRNA splicing experiments.

We cleared up the database, weeded out the junk and non-constitutional mutations, and then set up a system of criteria to define variants. We used the set of the 120 or so most frequent, but unclassified, mutations to then test the criteria, 20 at a time – the database curator John-Paul Plazzer was instrumental in getting all the relevant literature together for us. Then long international teleconferences, accommodating people in all time zones around the globe, after which we would re-consider the criteria and go again with the next 20, and so on. “Modified Delphi process” they call it. Early on we realised we needed a specialised sub-group to work on the issue of so called functional assays – RNA and protein expression models in the test tube. When we were finally happy with a set of criteria, we were then allocated 50 unclassified variants each, and in one evening between us we sorted out the remaining ones. After a bit more cleaning up of the data, we realised we had classified all 2,360 variants on the InSIGHT database, even if we could only say they were Class 3. But we found we had two sorts of Class 3s – ones with not enough data to go on, and those which despite a load of data resolutely stick in Class 3. What does this mean? Is it evidence that there are variants with truly reduced pathogenicity/incomplete
In this edition, our 10 minute interview is with Professor Sir Bruce Ponder, Li Ka Shing Professor of Oncology and Director of the Cancer Research UK Cambridge Research Institute. Professor Ponder has and continues to lead pioneering research to identify novel cancer susceptibility genes. Much of the genetic testing that we are able to offer today and how we run our familial cancer clinics is as a result of Professor Ponder's ground-breaking and highly innovative research.

Professor Ponder, for the younger members of CGG can you tell us what it was like in early 1990's when you were undertaking your research which successfully identified genes such as BRCA1, BRCA2, and RET?

In the late 1980's early 1990's, the focus in cancer genetics research was on linkage and identification of genes for the major inherited cancer syndromes. It was quite competitive, I think because there was so much luck involved. We used to say linkage was like throwing darts at the board blindfold and hoping for a bulls-eye. I am proud to have co-founded and chaired the International Breast Cancer Linkage Consortium which brought together almost all of the major groups around the world. This collaboration accelerated progress in gene discovery, and also collected the accurate clinical data which led to recommendations for the management of families.

What lead you to become interested in cancer genetics, rather than other areas of research in oncology?

I was interested in cancer genetics from the start of my career, in the mid 1970's. Even then it seemed to me that genetics had to be an important part of cancer and that if one could find the genes involved, one might understand the mechanism.

To begin with, I didn’t build a programme in genetics because we didn’t have the tools to map genes. But in 1980, I came across two MEN2 families in the Thyroid Clinic at the Royal Marsden. I had read the recent papers about the use of RFLPs for gene mapping, and I saw the opportunity both to map the genes, and to start a Familial Cancer Clinic.

In such a distinguished and exemplary career, has there been a particular highlight?

The highlights for me have been research discoveries. Helping to build a Cancer Centre in Cambridge has been interesting; but it doesn’t match the excitement of a new result in the lab. Finding RET as the MEN2 gene and completing the first cancer GWAS were both highlights. But most exciting was the moment (in 1987) when I looked down my dissecting microscope at a whole mount of mouse intestine, and saw the scatter of "descendant clones" that I had induced by mutation in the embryo and marked so that they were visible in the adult.

Where do you see cancer genetics research going in the future?

The somatic genetics of the evolution of cancer and its implications for therapy will be an important field for years to come. I hope and expect that we will be able to extend that analysis to pre-invasive disease. In germ line genetics I think polygenic susceptibility will be the major theme not just in cancer, but across all of medicine, in the next twenty years. Progress is slow, and some doubt we will ever find the way through the complexity. I am putting my money on gene regulatory networks as the way to understanding what is going on.

penetrance? We have reason to believe such variants are out there, but have we found a way of defining them? Which then begs the question, is a variant with a probability of pathogenicity >50% clinically actionable? There is no shortage of further work to do and concepts to explore!

The outputs from all this are now available at http://www.insight-group.org/variants/database/ and http://www.insight-group.org/variants/classifications/ with the current criteria at http://www.insight-group.org/criteria/ . We want more data and for everyone to submit all the variants they have found. The InSiGHT Variant Interpretation Committee ("VIC") will be happy to consider all newly submitted variants and give a classification. The bit of information you hold on a variant may hold the key to interpreting it for the world! Discussions are ongoing between the NHS DMuDB and InSiGHT as to how best to share the UK’s MMR gene data for greatest effect. The ACGS Best Practice guidelines on MMR analysis in LS are also currently being revised.

Finally, the paper itself “Application of a 5-tiered scheme for standardized classification of 2,360 unique mismatch repair gene variants in the InSiGHT locus-specific database” is now out in Nature Genetics at http://dx.doi.org/10.1038/ng.2854 . Incidentally, anyone who submitted a variant to the InSiGHT database has a micro-attribution under the ORCID system (www.orcid.org), i.e. they may cite this paper on their CV, an incentive we hope will encourage future submissions. And, if anyone else wishes to use what we’ve done to help with interpreting mutations in their favourite genes then we would be very pleased. Any questions, just ask.
"...the public will need to understand better the concepts of probability and risk..."

What are your current areas of research?
I am just restarting my lab after setting up the new CRUK Cambridge Cancer Institute. Following up our breast cancer GWAS in 2007, I am using a gene regulatory network approach to understand how individual SNPs impact the networks within the cell and thus contribute to susceptibility. I am also looking at the distribution of GWAS hits across the network, to get a sense of the degree of heterogeneity in mechanisms of susceptibility.

How do you see the role of cancer genetics evolving in the future, in particular with regard to liaising with other medical specialties?
New expertise relevant to common diseases tends to diffuse in time into the more general clinics and ultimately into primary care. The whole point of polygenic susceptibility, compared with the rare Mendelian syndromes, is that it potentially involves the whole population. So the management of the related risks will, eventually, necessarily be based in public health, primary care, and in disease-specific clinics. There will of course always be rare and complex cases which need the specialist knowledge of the dedicated genetics clinic.

Do you think we will enter an era whereby we are able to ‘profile’ an individual’s genetic cancer risk and then able to suggest lifestyle changes or offer medical interventions to modify this risk?
We can already offer some sort of “profile” of an individual’s genetic risk of some common cancers. How useful it is, depends on the action that can follow. As our knowledge of the genes, and of methods of intervention, increase, so the utility will probably increase. But there are still many issues to address. Do people understand probability sufficiently to make informed choices about interventions? How will we design the studies (necessarily long-term, and involving large numbers of people because the individual risks are likely to be quite small) to demonstrate that a particular intervention is effective?

Now that the ‘major’ cancer genes have been identified how do you see the future for further cancer gene identification, or are we moving more toward an era of investigating the clinical applications of your discoveries?
It is probably true that most of the strongly predisposing Mendelian cancer genes have been identified, although there is still the unknown yield that will come from the discovery of rare variants by DNA sequencing. I think, as I have said, that the future will move towards polygenic susceptibility. But of course those ‘polygenes’ may also have an important impact on the penetrance and phenotypic spectrum of the ‘major’ genes, sufficient to be of clinical importance.

Some of the genes you have identified are the most widely known among the general population. What role do you think we should play, as a profession, in increasing the general understanding of genetics and its implications within the general population?
As we extend genetics to larger sectors of the population, the public will need to understand better the concepts of probability and risk: for example, simple ideas such as that a 30% increase in a small risk, is still a small risk. We need to begin at school. In the shorter term, maybe journalists, politicians, and our medical colleagues would also be a good start. As geneticists, we should be ready to join in discussions on these issues.
Dates for your diary

Andrew Cuthbert

This year the UK / Dutch Clinical Genetics Societies and Cancer Genetics Groups Spring Conference is in the Netherlands on 17th – 19th March, Stadsgehoorzaal Leiden. The CGG conference is on days 1 and 2. Day 3 is just for the Dyssmorphology Club. See www.bsgm.org.uk for further details.

Manchester is this year’s venue for the regular and excellent Cancer Genetics Course. It’s on 30th April to 2nd May. For further details please send emails to Dr Lalloo at fiona.lalloo@cmft.nhs.uk.

Deadline for contributions for next issue is 30 April 2014

Emma Woodward
Clinical Genetics Unit
Birmingham Women’s Hospital
Metchley Park Road
Edgbaston
Birmingham B15 2TG
Phone: +44 121 627 2630
Email: e.r.woodward@bham.ac.uk

Andrew Cuthbert
West Midlands Family Cancer Service
Clinical Genetics Unit
Birmingham Women’s NHS Foundation Trust
Birmingham B15 2TG
Phone: 0121 627 2630
email: andrew.cuthbert@bwhct.nhs.uk
Officers of the BSGM and constituent societies

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<td><a href="mailto:sandra.birdsall@wales.nhs.uk">sandra.birdsall@wales.nhs.uk</a></td>
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