BSGM
The British Society for Genetic Medicine

The Newsletter of
The British Society for Genetic Medicine

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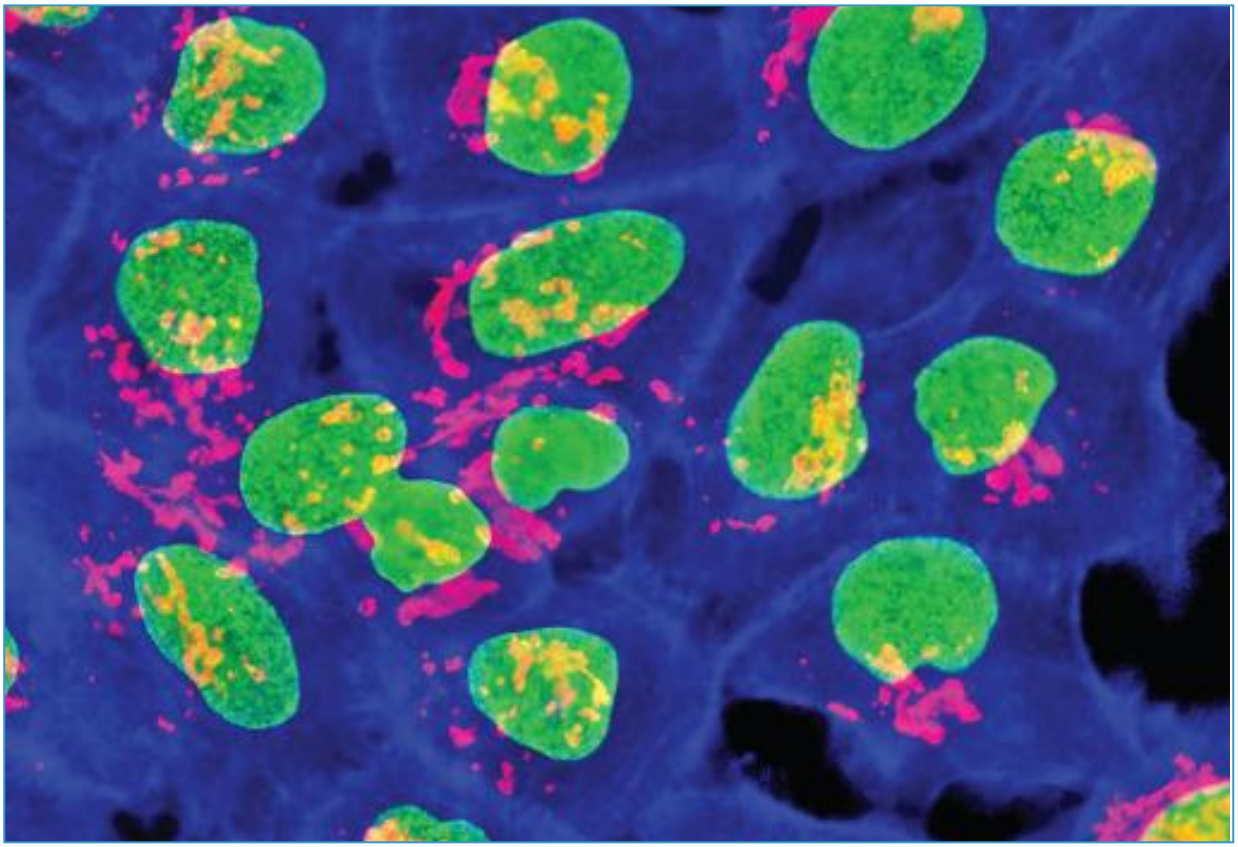
BSGM News



Human Skin Epidermoid Carcinoma Epithelial Cells (A-431) © Michael W Davidson, National High Magnetic Field Laboratory, Florida State University
(http://micro.magnet.fsu.edu/primer/techniques/fluorescence/gallery/cells/a431/a431cellslarge.html)

From the newsletter editor

Welcome to this issue of the BSGM News. A few things that you will note about this newsletter - Firstly, this issue is being published much later than advertised. This was originally to allow for contributions following the ESHG meeting in June. However this has been compounded by a change to how the newsletter is being published, which is why there is a different look to this issue. It is anticipated that this will be one of the final issues of BSGM News which is published in this format. This has also been a 'home grown' effort by the editorial team to not only curate the articles, but to also put on their publishing hats and format the issue. We appreciate that the look and feel of the newsletter is different to what we have published in the past, however the quality of the articles is still just as high.

This issue also sees the final message from our past chair, Angela Douglas. I would like to take this opportunity to thank her for all her support during her tenure. You will hear from Bill Newman, our new chair, in the next issue.

As ever we rely on BSGM members to identify topics that may be of interest to the entire membership. Please get in touch if you have any ideas for future articles or features. My contact details can be found at the end of the first section

Michelle Bishop

Outgoing Chair's Report

Angela Douglas, Chairman BSGM

This year has been a very busy one and we are only half way through. In December last year we saw the 11 Genomic Medicine Centres in England designated and launched and the 100,000 Genomes Project get under way. These Centres have proved themselves through a rigorous competitive tender process and have come through as centres of excellence that meet the stringent requirements to deliver the project. We have all been watching and hearing about their progress delivering whole genome sequence results to patients, and pondering the future of this genomic revolution.

The BSGM welcomed another Special Interest Group into its fold, the Association for Inherited Cardiac Conditions (AICC) and we look forward to closer working relationships with both the Cardiac Geneticists and Cardiologists with a special interest in Genetics. We also welcomed 40 more new members from Genetic Services.

It has not all been plain sailing. We have had more than our fair share of financial challenges, and thanks to the hard work, resourcefulness and determination of our new Treasurer, Professor Peter Farndon, the BSGM will break even at the end of the 2015/16 financial year, but only just. We also owe a big debt of gratitude to the continued support of all the constituent groups that make up the BSGM. This financial turnaround has only been possible through the agreement of the Membership to accept the accounts for the past year, to accept the new working accounts and accept an emergency resolution (and yes we were quorate with just under 60 members present and a unanimous vote from all members present at the AGM in June 2015 in Glasgow).

Emergency Resolution: An additional £5 was added to subscriptions for BSGM (except students) this year.

To ensure the BSGM moves forward in a more financially stable position it was also agreed that:

- A new governance framework would be developed, adopted and monitored by the BSGM Council.
- The BSGM constitution and structure of Council would be reviewed to ensure they meet the needs of an umbrella organisation and the constituent groups.
- Job descriptions would be developed for officers and council members and regularly reviewed (annually).
- Measures would be put in place to ensure 'corporate memory' would be developed with papers archived to ensure knowledge is shared with new Council Executives.
- The electronic system for membership, administration and subscription collection will be completed with urgency
- The Direct Debit subscription collection system will be updated with urgency; cheques and credit card transactions in the office phased out in favour of an online PayPal facility.

Outgoing Chair's Report *cont…*

- A strategic plan will be developed leading to a rolling programme of implementation with dates for delivery.
- Standard Operating Procedures for the administration office will be agreed with the Executive Officer, recorded and monitored.
- Regular and detailed reports of financial matters, including performance against budgets, to be placed before Trustees and Council.
- A website strategy and policy will be developed and reviewed, and in addition a monthly plan developed for updating material.
- An online system for collecting items for the newsletter and its publication will be developed urgently.
- The office move is to be completed, including archives created with a personal data retention policy developed.

With the implementation of the above strategies the BSGM will hopefully mitigate the risk of any future financial challenges, and become more sustainable and relevant.

On a more positive note the BSGM has been extremely active this year nationally, raising the profile of the Genetics body through:

- Being a member of the **Genomics England** Clinical Advisory Group – Roll out of 100,000 Genomes Project.
- Working with **NHS England** advising on the optimisation of protocols for the 100,000 Genomes Project.
- Advising **NHS England Commissioning** arm on the specification for Genomic Laboratories redesign.
- As part of the **PHG Foundation** working groups which produced the:
    - *Releasing Genomics* report and involved in the implementation of the recommendations. On a side note, if you haven't seen this document yet, we recommend you take a look at this excellent piece of work.
    - *New genomic technologies and pregnancy* convened by the Joint Committee for Genomic Medicine.
- Advised **HEE** on the content of the new MSc in Genomic Medicine and CPPD training in Genomics, ensuring our workforce will be fit for the future.

The BSGM has also been working with the Department of Health (DH) through:

- Developing a plan to have a Rare Disease Registry under Public Health England, the hosts of the current Cancer Registry.
- Advising on policy for data sharing across the NHS.
- Working as part of the European Reference Network – Looking at data sharing across the EU (EU Commissioned work).
- Advising on ethics and bioethics – DH Group (Mark Bale and Colin Pavelin)
- Working with Dr Ian Barnes on the Pathology Quality Assurance – Barnes Report

In addition the BSGM has been representing the Membership on the following committees:

- UKGTN (UK Genetic Testing Network)
    - Gene Dossiers
    - GENUs
- CRG (Clinical Reference Group)
    - National Dashboard
    - Informing Commissioning
- NICE
    - Advising on new guidance (Breast and ovarian cancer, CF)

The BSGM has also been providing advice and support through:

- Local conferences and meetings
- BSGM newsletters
- Developing the new BSGM website
- The Scientific Committee who worked with the ESHG on the 2015 conference program
- Communicating with new members and member groups – 'Growing the Membership'
-

So as you can see it has been a very busy time.

Finally, I would personally like to thank all the BSGM Council for their continued support. I would also like to thank you all, the membership of the BSGM, for all your support and encouragement. It has truly been an honour and a pleasure being your Chairman. As my last duty as Chairman, I would like to:

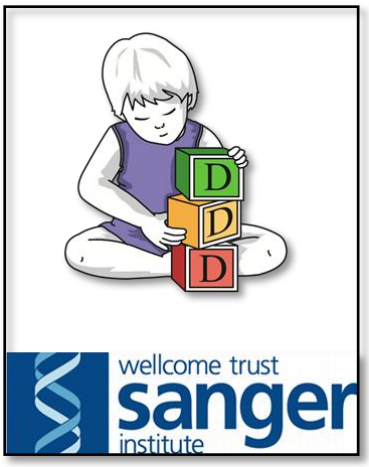
Welcome Bill Newman
New Chairman of the BSGM

I look forward to working with Bill, in my capacity as the new Vice Chair of the BSGM and I wish the BSGM continued success under Bill's leadership. I believe the BSGM will be in very experienced, safe and competent hands. My very best wishes to you

Outgoing Chairman BSGM

If you know it, I'd like to know it too

Dr Anna Middleton
Principal Social Scientist, DDD project, Wellcome Trust Sanger Institute



How might people want to use genomic technology? Are they even interested in it? These are questions that formed the heart of the GenomEthics study, our social sciences research from the Wellcome Trust Sanger Institute, part of the Deciphering Developmental Disorders project.

Despite a lot of rhetoric, we don't really know how potential research participants want to engage with researchers in sequencing studies. Answering this requires the delivery of social sciences research in multiple ways, with multiple populations. Our survey (see www.genomethics.org) of nearly 7000 people from 75 different countries shows that 98 per cent want to be informed if researchers using their genetic data stumble upon indicators of a serious preventable or treatable disease. Our sample consists of members of the public, genomic researchers, genetic health professionals and non-genetic health professionals and we asked them to image they were participating in sequencing research. We clearly explained what this might involve through 10 short films embedded in the survey. The films also described some of the ethical issues raised by sequencing technologies. The study contributes to an important and on-going conversation about the perceived responsibilities of researchers to return individual results to participants.

We discovered that genomic data has an inherent value to participants even if it is not currently clear what the information means for health outcomes. We also found that genetic professionals surveyed were concerned about returning data that cannot yet be interpreted accurately. The majority of participants wanted to receive information about serious conditions, even if the risk of developing the condition was as low as 1 per cent.

The validity of our survey findings is contentious – do attitudes towards a hypothetical scenario actually predict what people would do in reality? It is difficult to know, but the last 50 years of health psychology research offer strong arguments to suggest that attitudes are one of the best predictors of behavior. Until large scale studies exist that return volumes of genomic data to participants, we cannot evaluate what people choose to do in practice; however, what we can do is ask them what they think they might do.

When we asked Alastair Kent OBE, Director of Genetic Alliance UK, for his views on the return of results from sequencing studies, this is what he said: "we asked patients and families how much they want to know about their genetic information; their immediate reaction was that whatever information the researchers or clinicians found out, they wanted to know too. But there can be no one size fits all. We need to make sure that there is enough information and support available to allow individuals to make an informed choice about what is right for their situation. We need to remember this information belongs to the individual and they should be able to decide for themselves what they do and don't find out about their health – which means we need to start thinking about how this can be recognised."

Our survey data shows that genetic health professionals (clinical geneticists, genetic counsellors and diagnostic clinical scientists) were five times more likely than other groups to think that incidental findings, results that are not the main focus of a research project but may be of clinical importance, should not be returned. Both genetic health professionals and genomic researchers were more likely to think that information about ancestry should not be shared.

Genetic health professionals are acutely aware of the challenges posed by interpreting genetic information accurately and communicating results to patients. There are still so many unknowns; having key indicators for a disease in your genetic code may not necessarily mean that you will develop that disease. Much of the information in our personal genetic codes is currently uninterpretable and of uncertain clinical significance. It will take many years of research before we know how to use much of this data for clinical benefit.

The survey was conducted as part of the Deciphering Developmental Disorders (DDD) project, which seeks to find genetic diagnoses for rare developmental disorders using patients' sequence data. The DDD project did not search this data for unrelated disease

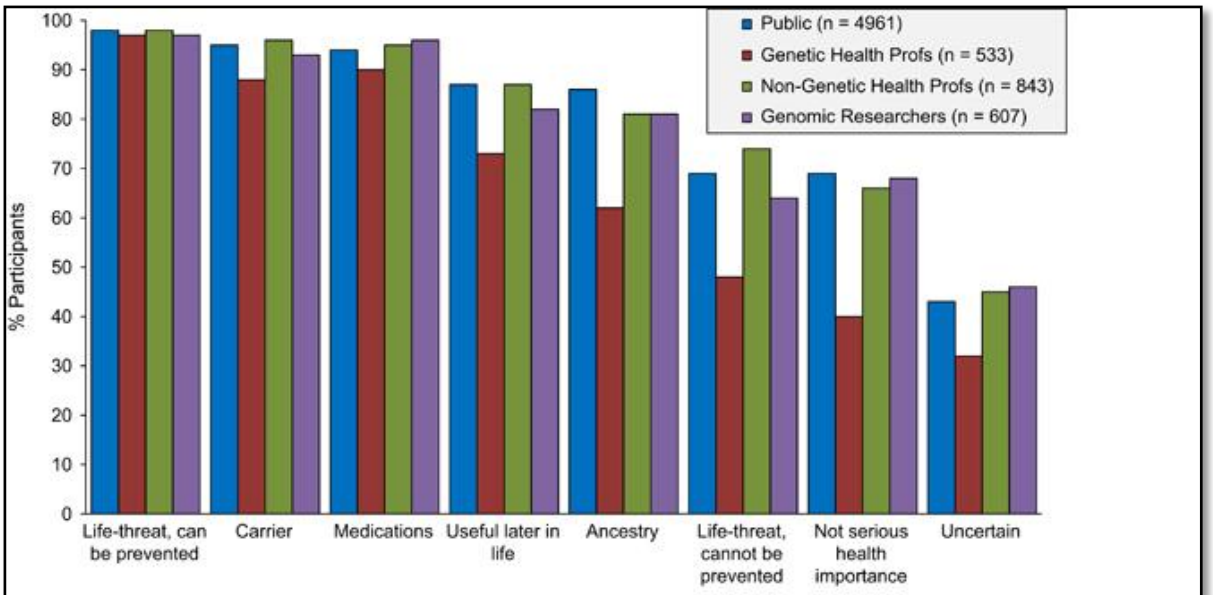
If you know it, I'd like to know it too *cont…*

indicators and only returned results likely to be linked to the patients' developmental disorders. This position is supported by the findings of the survey as, while participants were keen to learn their genetic results, the majority did not think researchers should be **required** to actively search for additional indicators of disease, unrelated to the study aims, **if** it compromised the ability of researchers to answer their research question. Thus, if we have a situation where looking for additional disease indicators is easy, cost effective and clinical partners are engaged and willing to delivery results and follow up findings, our research has certainly shown that research participants would be supportive of having a whole collection of results returned to them.

We have published 6 papers to date on the above work, a blog and film on our work is here: http://bit.ly/1d0w7dh

Main study results can be found here:

Middleton A, Morley K, Bragin E, Firth HV, Hurles M, Wright CF, Parker M on behalf of the DDD study (2015) Attitudes of nearly 7000 health professionals, genomic researchers and publics toward the return of incidental results from sequencing research European Journal Human Genetics. Epub ahead of print: 29th April online. doi: 10.1038/ejhg.2015.58

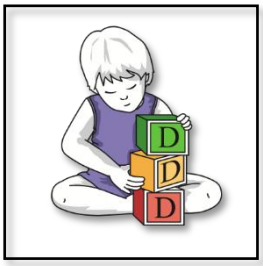


Q: If you had the choice to receive information in the following categories, what would you want to know?

Life-threat, can be prevented = conditions that are life-threatening and can be prevented; carrier = tells me if I'm a carrier of a condition that could be relevant to my children; medications = demonstrates how I might respond to different medications or drugs (e.g. statins, anti-depressants etc.); useful later in life = information that is not immediately relevant but could be useful later in life (e.g. relating to a very late onset cancer or predisposition to strokes); ancestry = tells me about my ancestry; life-threat, cannot be prevented = conditions that are life-threatening and can be prevented; not serious health importance = is not likely to be of serious health importance (e.g. mild eyesight problems); uncertain = information that is uncertain and cannot be interpreted at the moment

DDD Study Progress Report

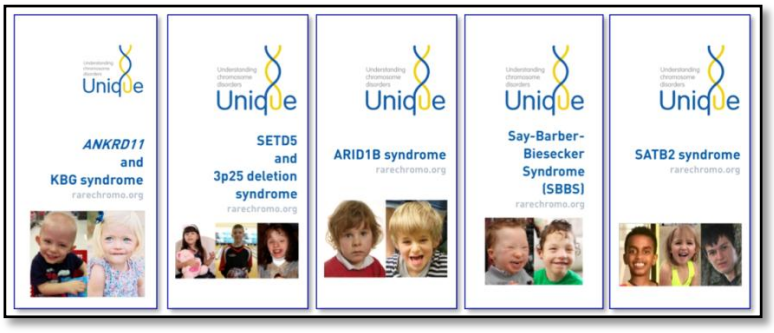
Caroline Wright
on behalf of the DDD Study
Wellcome Trust Sanger Institute



In the four years since its start in April 2011, the UK-wide Deciphering Developmental Disorders study (DDD) has **recruited nearly 14,000 children** with severe undiagnosed developmental disorders and their parents – almost 2,000 more than expected! This incredible feat was achieved through the hard work of all 24 Regional Genetics Services in the UK and Ireland, supported by a dedicated team of scientists at the Wellcome Trust Sanger Institute in Cambridge.

Now that recruitment has come to an end, we are focusing on completing the initial phase of the project. Samples are still flowing in until September 2015, and we expect to have processed over 45,000 samples by the end of the year. We have finished all the array-CGH experiments, with data generated on around half the probands, and aim to exome sequence every proband and around 10,000 trios (child, mum and dad) by early 2016. Results from our first 1,133 trios have now been published in the *Lancet* (PMID: 25529582) and *Nature* (PMID: 25533962). We are now analysing data from 4,295 trios and we anticipate achieving a diagnostic yield of >30% in these trios, as well as discovering multiple new recessive and dominant developmental disorder genes and pioneering novel analytical methods.

Our Developmental Disorder Genotype-2-Phenotype (DDG2P) database now contains over 1,400 published gene-disease pairs and, together with minor allele frequencies and predicted consequences for each variant, forms a key part of our analytical pipeline. As new genes are identified, the DDG2P list will expand, enabling new diagnoses to be made on data generated earlier in the study. Plausibly pathogenic variants in known developmental disorder genes will continue to be returned to clinical teams for validation and communication with the family, and those in non-disease genes will be shared publicly via a dedicated 'DDD research track' in DECIPHER (https://decipher.sanger.ac.uk), thus increasing our power to make new diagnoses. In addition, all our data are available to researchers via the European Genome-phenome Archive (https://www.ebi.ac.uk/ega) under a managed data access agreement.



In addition to the primary research led by the Wellcome Trust Sanger Institute, the DDD study now has over 100 complementary analysis projects led primarily by members of the regional genetics services and focused on specific genes or phenotypes. Several of these have now been published, often as part of a larger cohort of children from around the world with pathogenic variants in the same gene. Many clinicians have also helped to write patient information leaflets for new single gene disorders, which are now available through the patient support group *Unique* (http://www.rarechromo.org), and we are hoping to facilitate many more in future. Our social science study investigating public attitudes to data sharing in genomics has also resulted in numerous publications, and the online videos developed to support this project continue to play an important role in genomics education across a number of different countries (www.genomethics.org).

The next phase of the project will continue through to 2021, and will include whole genome sequencing and other extended investigations of DDD families who remain undiagnosed after exome sequencing. We are working with partners, including Genomics England, to ensure that we maximise the benefits of this study for patients both now and in the future.

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

RAPID update: Non-invasive testing for single gene disorders

Melissa Hill, Suzanne Drury and Lyn Chitty on behalf of the RAPID team

**North East Thames Regional Genetics Service and
Genetics and Genomic Medicine, UCL Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust**

Introduction

The NIHR funding for the RAPID Programme, which has been running since July 2009, will officially come to an end in September, but we have secured further funding to continue both sample collection and the work to develop non-invasive prenatal diagnosis (NIPD) for single gene disorders. So don't stop recruiting!

There is no doubt that we have achieved one of the major objectives of RAPID in developing the standards required to implement NIPD for some single gene disorders and, as a result, we are transforming the way prenatal diagnosis is offered to families at high risk of genetic disorders. An audit of the prenatal molecular diagnosis service at the North East Thames Regional Genetics Laboratory (NETRGL) showed that 32% of our diagnostic tests were done using NIPD (67% if fetal sex determination was included).

Our success in developing NIPD is in no small part due to our collaboration with genetics and fetal medicine units around the UK. There are now over 40 centres contributing samples to the RAPID sample collection at NETRGL. We have parental and fetal samples collected from both normal and complicated pregancies, with over 9500 maternal (~1500 aneuploid and 1300 single gene disorders) and 4500 paternal samples.

The RAPID team, in collaboration with colleagues from around the country, have looked at all aspects of developing and implementing NIPD for single gene disorders including development of laboratory protocols[1,2,4,10,11,12], consultation with stakeholders[5-9], consideration of ethical issues[3] and cost analyses[11]. Here we provide a brief update on our progress in developing NIPD for single gene disorders.

NIPD for single gene disorders

Differentiating maternal and fetal alleles against a high background of maternal cell free DNA in maternal plasma has been the key challenge for developing NIPD for single gene disorders. Accordingly, the first successful applications have been in scenarios where the allele is not present in the mother but could be present in the fetus such as paternally-inherited single gene disorders, or single gene disorders arising *de novo*, such as achondroplasia or thanatophoric dysplasia. There are also several examples in the literature of NIPD being used for autosomal recessive conditions if the parents carry different mutant alleles, by excluding the presence of the paternal mutant alleles in maternal plasma. If the paternal allele is identified, an invasive test is required to determine whether or not the fetus has inherited the maternal allele.

The most difficult NIPD tests to develop are those for X-linked conditions or autosomal recessive conditions where parents carry the same mutation as the mother's own alleles must be taken into account before accurate fetal diagnosis can be made. Using next generation sequencing (NGS), which allows accurate quantification of specific sequences, proof-of-concept studies have been performed for a number of conditions using approaches such as relative mutation dosage (RMD) or analysis of single-nucleotide polymorphisms (SNPs) by whole genome sequencing and relative haplotype dosage analysis (RHDO). These tests have not yet entered clinical practice primarily due to practical limitations such as estimating fetal fraction, time requirements, costs and the need for a high proportion of cffDNA in the sample.

Progress made by the RAPID team

NIPD for the autosomal dominant conditions achondroplasia, thanatophoric dysplasia and apert syndrome, which were first offered at NETGRL on a research basis in 2011, were initially performed with PCR and restriction enzyme digest[1,4], but these assays have been superseded by NGS panels which allow non-common mutations to be included in the same assay and if new mutations are found, they can easily be incorporated into the assay.[10] Alongside fetal sex determination, these assays increasingly form a large component of the prenatal diagnostic service at NETGRL (Table 1). Gene dossiers have been approved for all three NGS assays.

	Fetal sex	Achondroplasia	Thanatophoric dysplasia	Apert syndrome
2010-11	103	13	-	3
2011-12	124	14	2	2
2012-13	163	22	11	3
2013-14	169	14	18	5

Table 1: NIPD performed at NETGRL for fetal sex determination and for the diagnosis of Achondroplasia, Thanatophoric dysplasia and Apert syndrome.

An NGS assay to detect ten common CF mutations for exclusion of the paternal mutation has been developed.[11] This assay is only applicable to couples who are known carriers of different CF mutations and the paternal mutation is one of the 10 mutations. This represents approximately 30% of CF carrier couples in the UK. Previous paternal exclusion assays for CF reported in the literature have been developed on a case-by-case basis, which is not ideal in a service laboratory where high-throughput assays testing multiple cases or multiple mutations in a single run are required to optimise turnaround times and minimise costs. Our NGS assay addresses these issues and we are working on extending the number of mutations included in the panel which will make this test of use to more families. To date, six tests have been successfully performed. The gene dossier for this assay was approved in 2014. An NGS assay for the direct diagnosis of CF when parents carry the same mutation is being developed.

A number of bespoke tests for individual families have been performed at NETGRL on a case-by-case basis. These include; Crouzon syndrome, Frasers syndrome, Autosomal recessive polycystic kidney disease, Zellweger syndrome, SMARCB1 and Osteogenesis imperfecta (Table 2). A gene dossier for the diagnosis of Crouzon syndrome has been submitted. We are able to develop NIPD on an individual patient basis but ideally development should be done prior to pregnancy as working up a test can take up to eight weeks. Please contact Lucy Jenkins (lucy.jenkins@goish.nhs.uk) or Sarah Mason (sarah.mason@gosh.nhs.uk) to discuss practicalities and costs.

Condition	Number of NIPD tests performed
Autosomal recessive polycystic kidney disease	1
Crouzon syndrome	1
Frasers syndrome	3
Osteogenesis imperfecta	2
Neurofibromatosis	1
Rhabdoid tumour predisposition syndrome	1
Torsion Dystonia	4
Tuberous Sclerosis	1
Zellweger syndrome	1

Table 2: Examples of NIPD tests for single gene disorders performed at NETGRL.

Disorders caused by mutations in genes with known pseudogenes, such as CAH or SMA, cannot be directly sequenced in cffDNA based assays. We have used CAH as a model disorder for NIPD for autosomal recessive conditions and situations where NIPD is complicated by the presence of a pseudogene. An NGS based assay for the diagnosis of CAH has been developed using a haplotyping approach termed relative haplotype dosage analysis. Using this approach the actual mutation does not need to be detected in the fetus, just inheritance of the high risk allele. Thousands of SNPs surrounding the gene of interest are captured and sequenced in parental and proband samples; parental and proband haplotypes are determined and the fetal genotype can then be inferred. A gene dossier was submitted in January 2015.

NIPD for the haemoglobinopathies (sickle cell disorder and beta thalassaemia) is being developed. We have moved on from digital PCR[2] and are now developing an NGS based assay for sickle cell disorder and beta thalassaemia.

NETGRL is the UK's only acredited laboratory currently delivering NIPD as a prenatal diagnostic service for single gene disoders. We also receive referrals regularly from overseas. We are keen to continue to expand this service as it is clear that women who have had NIPD and parents at risk of single gene disorders, as well as health professionals, all welcome the additional safety achieved through decreasing need for invasive testing, earlier availability and hence potential for improved access NIPD brings[5-9]. Stakeholders have emphasised the need for NIPD for single gene disorders to continue to be offered through specialist genetic or fetal medicine services.

This would ensure appropriate pre-and post-test counselling offered by health professionals with specialist knowledge of the condition and experience and training in counselling for prenatal testing.[5-9]

It is likely that the cost of NIPD overall will be greater than traditional testing and a detailed economic analysis is ongoing. One factor that may influence cost is the requirement to sequence both parents and an affected proband for some recessive disorders, as well as the need to identify heterozygous SNPs in parents to measure fetal fraction for definitive diagnosis in recessive and X-linked conditions. Another factor is the likely increase in uptake of prenatal testing to inform post-natal management for those couples who would like to know if the child is affected but would not have previously put their pregnancy at risk with an invasive test. For example our survey of potential service users showed that interest in NIPD for CF was high, with 90% reporting they would have NIPD if it was available, compared to 43.5% who would currently consider invasive testing.[11]

RAPID resources

The RAPID website (www.rapid.nhs.uk) was updated recently and is a valuable resource for patients and health professionals wanting to learn more about cffDNA, NIPD and NIPT.

For health professionals interested in offering NIPD please contact us at rapid@ucl.ac.uk or visit the RAPID website (www.rapid.nhs.uk) for information sheets for both health professionals and patients.

Looking to the future

While the RAPID programme ends in September 2015, we anticipate other funding will be used to continue growing the RAPID/SAFE sample collection and we have a GOSH BRC funded scientist to continue the development of NIPD for single gene disorders.

The RAPID dissemination meeting will be held at the Institute for Child Health in London on September 15 2015, please contact us at rapid@ucl.ac.uk for details. The meeting will be accredited for CPD. Staff who have assisted with the RAPID project will be given priority but others may register.

RAPID publications focusing on NIPD for single gene disorders

1. Chitty LS, Griffin DR, Meaney C, et al. *Ultrasound Obstet Gynecol* 2011; 37(3): 283-9.
2. Barrett AN, McDonnell TC, Chan KC, Chitty LS. 2012; 58(6): 1026-32.
3. Deans Z, Hill M, Chitty LS, Lewis C. *Eur J Hum Genet* 2012; 21(7): 713-8.
4. Chitty LS, Khalil A, Barrett AN, Pajkrt E, Griffin DR, Cole TJ. *Prenat Diagn* 2013; 33(5): 416-23.
5. Hill M, Karunaratna M, Lewis C, Forya F, Chitty L. *Am J Med Genet A* 2013; 161A(7): 1612-8.
6. Hill M, Compton C, Karunaratna M, Lewis C, Chitty L. *J Genet Couns* 2014; 23:1012-21.
7. Lewis C, Hill M, Chitty LS. *Clin Genet* 2014; 85(4): 336-42.
8. Hill M, Suri R, Nash E, Morris S, Chitty LS *Journal of Clinical Medicine* 2014; 3(1): 176-90.
9. Skirton H, Goldsmith L, Chitty LS. *Eur J Hum Genet* 2014; Nov 5 epub.
10. Chitty LS, Mason S, Barrett AN, et al. *Prenat Diagn* 2015 Feb 26 epub.
11. Hill M, Twiss P, Verhoef TI, et al. *Prenat Diagn* 2015 Feb 24 epub.
12. Drury S, Lo K, Boustred C et al. *Manuscript in preparation.*

Translation of non-invasive prenatal diagnosis (NIPD) for selected single gene disorders into a clinical setting: the NIPSIGEN project

Stephanie Allen, Michael Parks, Samantha Court, Siobhan Cleary, Samuel Clokie, Julie Hewitt, Denise Williams, Trevor Cole, Fiona MacDonald and Mike Griffiths

West Midlands Regional Genetics Service

The NIPSIGEN project is now two years into the three year project funded by the Health Innovation Challenge Fund (HICF). The aim is to develop and validate NIPD for selected single gene disorders (SGDs) as an alternative to invasive tests such as chorionic villus sampling and amniocentesis which have an associated risk of miscarriage. Cell free fetal DNA (cffDNA) derived from the placental trophoblast is present within a maternal blood sample and can be utilised for non-invasive prenatal diagnosis (NIPD).

The project took advantage of the Musketeer's memorandum, the first project to be administered under the consortium agreement that enables all regional genetics centres to recruit without requiring submission for ethical approval at individual sites. This has enabled women with a pregnancy at risk of having a baby affected with Duchenne or Becker muscular dystrophy (DMD/BMD) to be recruited nationally.

After testing various methods, we have successfully established a prenatal test for NIPD of DMD/BMD. This method uses next-generation sequencing and relative haplotype dosage to determine which of the mother's dystrophin gene alleles is inherited by a male fetus. Over a thousand single nucleotide polymorphisms spanning the entire dystrophin gene are sequenced from a previously affected child to identify the mutated haplotype. Over-representation of one of the haplotypes in maternal plasma from the current pregnancy indicates which DMD allele has been inherited by the fetus. Experimental data on cffDNA derived from 10 maternal blood samples of a pregnant control group and patients recruited who are pregnant and at risk of having a baby with DMD/BMD has yielded promising results with a high sensitivity and specificity. Test validation is on-going as new patients are recruited to the study. It is also important for this approach that we collect DNA from an affected male sibling where available. We therefore requested this as an amendment to the consent form and this has gained ethical approval.

In addition to its robustness, the test is affordable (on par with current costs for prenatal diagnosis of DMD/BMD) and can be modified to include other SGDs. We are therefore extending the testing to include other disorders – in particular spinal muscular atrophy (SMA) and congenital adrenal hyperplasia (CAH). A further amendment to the NIPSIGEN study has been agreed to recruit nationally for SMA, in addition to the patients we have been recruiting locally within the West Midlands region.

Our aim for the final year of the study is to complete validation of testing for DMD/BMD, and to develop and validate testing for SMA and CAH.

Recruitment update: Nationally 34 patients have been recruited with a pregnancy at risk of DMD/BMD. Of these 17 were female fetuses, 13 male, and we are awaiting the results of 4. We have recruited 6 patients with a pregnancy at risk of SMA and 6 at risk of CAH, all from the West Midlands region. With national recruitment to the SMA group now being rolled out we hope to increase these numbers to enable validation.

We would like to thank all our national recruiters for sending samples and we will keep everyone informed as to when the testing is ready to be offered to patients.

RD-Connect: an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research

Louise Johnston[1] and Steve Laurie[2] on behalf of the RD-Connect consortium.

[1]The John Walton Muscular Dystrophy Research Centre, MRC Centre for Neuromuscular Diseases, Institute of Genetic Medicine, Newcastle University
[2]Centro Nacional de Análisis Genómico, Barcelona, Spain

The rare disease environment and impact of new technologies

Although individually uncommon, rare diseases – defined in the European Union as those with a prevalence of less than 5 in 10,000 and in the US as diseases that affect fewer than 200,000 US citizens – affect around 30 million people in Europe and the US and 350 million worldwide. Many rare diseases are chronic and life-threatening and are accompanied by substantial morbidity, an extensive healthcare burden, and considerable psychological and financial stress for affected families. Furthermore, many patients with rare diseases lack timely and accurate diagnosis and even fewer receive tailored treatments influencing survival and quality of life.

Over 80% of rare diseases have a genetic component, and for this reason particular emphasis has been placed on the prospects offered by the rapid development of next-generation genomic technologies such as whole-exome and whole-genome sequencing. The development of such high-throughput approaches has the potential to speed up diagnosis of known conditions, facilitate the discovery of new causative mutations, and offer new therapeutic avenues based on manipulation of the underlying genetic defect. Other omics approaches such as transcriptomics and proteomics are also increasingly being used in rare disease to increase our understanding of physiological and pathological processes, which in turn can be translated into novel diagnostic and therapeutic options for rare disease patients.

In order to make progress, the integration of the outputs of these new technologies with detailed clinical phenotype data and the combination of data across centres and across diseases is key. While such integrative efforts are ongoing within some medical centres, individual efforts often remain largely 'siloed'. This is a critical problem in rare disease studies, where a given centre may see only a small number of patients with a certain disease. Enabling such datasets to be linked across centres and across diseases is thus an essential step.

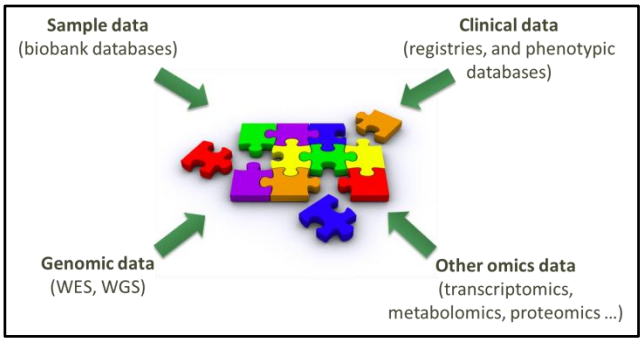


Figure 1. The RD-Connect platform. Connecting databases, registries, biobanks and clinical bioinformatics for rare disease research

In an attempt to address this issue, major medical research funders have come together in a global effort that aims to foster collaboration in rare disease research. The International Rare Diseases Research Consortium (IRDiRC) was launched in 2011 and now has 40 members from across the world, including the European Commission as well as key national funders such as several institutes from the US National Institutes of Health. Each of these funders has pledged to spend a minimum of US$10 million on rare disease research over five years. The IRDiRC has set itself two headline objectives to achieve by the year 2020: (i) to deliver 200 new therapies for rare diseases and (ii) to develop the means to diagnose most rare diseases.

Development of a unified informatics platform for data sharing and analysis

One of the first projects to be funded under the IRDiRC is RD-Connect (http://rd-connect.eu/). Initiated in 2012, RD-Connect is a €12 million infrastructure project funded by the European Union's Seventh Framework Programme. The project brings together 27 partner institutions and works in close collaboration with two associated research projects, NeurOmics (www.rd-neuromics.eu) and EURenOmics (www.eurenomics.eu).

RD-Connect *cont…*

RD-Connect is developing an integrated platform in which omics data is being combined with clinical phenotype information and biomaterial availability, accessible online and queryable with a suite of analysis tools (Figure 1).

Raw genomic data from collaborating projects is securely deposited in the European Genome-phenome Archive (EGA) before being processed through a standard pipeline to ensure cross compatibility of data from multiple projects. The processed data is then held in the central RD-Connect database, where it will be combined with other omics data types plus phenotypic and biomaterial information. Researchers approved by a data access committee will access data through a data coordination centre that enables comparison of datasets across projects and analysis with sophisticated bioinformatics tools.

The genomics side of the RD-Connect platform already includes over 360 next-generation sequenced exomes linked to detailed phenotypes stored in PhenoTips (https://phenotips.org/) using the Human Phenotype Ontology (HPO). Exomes were processed with the first version of the RD-Connect standard analysis pipeline for genomics, which exceeds 99% precision and sensitivity when compared to the National Institute of Standards and Technology (NIST) reference set of calls for NA12878. The platform runs on a Hadoop cluster and uses technologies such as ElasticSearch, Postgres, Scala and Angular.js, making it highly configurable and efficient. The exomes can be combined in a very flexible manner and variants can be filtered and prioritised through the user-friendly front-end using the most common quality, genomic location, effect, pathogenicity and population frequency annotations, including Combined Annotation Dependent Depletion (CADD) and The Exome Aggregation Consortium (ExAC). Moreover, additional tools can be integrated at the database level or at the interface through application programming interface (API) queries. To date, DiseaseCard, Alamut Functional Annotation (ALFA) and gene-disease relationships in nano-publication format have been integrated.

Current focus is on the integration of Exomiser (including PhenIX) to prioritize variants through genotype-phenotype queries, the provision of reliable allele frequencies, the lighting of a Global Alliance for Genomics and Health (GA4GH) beacon and patient matchmaking. A first official release including data from approximately 1000 exomes and access by any authorised researcher is expected by the end of 2015.

RD-Connect genomic analysis platform is opened for beta-testing

The platform is currently open for beta-testing by RD-Connect partner projects. Other users can register later this year. If you are interested in becoming one of the first users you should: (i) check your consent forms to make sure they allow data sharing for research purposes; (ii) ensure you have a detailed phenotype for each participant; (iii) ensure you have access to the BAM / FastQ files from your sequencing experiments.

Contact us at **platform@rd-connect.eu** for further information and to be notified when you can join the platform.

EU reforms put access to genetic testing in danger

Alison Hall

PHG Foundation

Medical devices regulations

Over recent years the European Union has undertaken major reforms to the way in which it regulates medical devices and *in vitro* diagnostic medical devices (which include blood tests and laboratory assays). These reforms are significant, since these Regulations will have a direct effect on Member States, unlike Directives which need to be enacted into national law. The *In Vitro Diagnostic Medical Devices Regulation* is likely to impact on health services such as the NHS in two major ways.

Regulation of genetic testing

For the first time, the scope of the proposed Regulation has been extended to specifically include genetic tests and to set out specific and onerous requirements for how genetic tests may be used. These include providing that genetic tests may only be conducted by medically qualified personnel; that genetic counselling must be provided before and after a genetic test is delivered; and that explicit written consent must be obtained before every genetic test is performed. Many organisations, including the PHG Foundation, are concerned that these requirements will restrict access to genetic tests and access to downstream diagnosis, targeted interventions and treatment. For example, in the UK, genetic tests are increasingly being offered by genetic counsellors or midwives as part of routine NHS care. If the legislation were to be adopted as currently drafted, clinical practice would have to be restructured to comply with the Regulation.

'In-house' test development

The existing Directive provides an exemption for tests developed 'in-house'. The proposed Regulation narrows the scope of that exemption: it provides that single health institutions have the possibility of manufacturing, modifying and using devices in-house, in order to address urgent or unmet medical needs for patients (including in rare disease diagnosis), which cannot be met by an available CE-marked device. However, devices (including genetic tests) which are manufactured within non-health institution laboratories and put into service without being placed onto the market are subject to the Regulation. What is unclear is whether commercial laboratories providing genetic testing services for the NHS can utilise this exemption. If not, the result could lead to additional bureaucracy and increasing costs of developing clinically useful tests.

One of our criticisms of the current proposals is that they assume that all genetic tests carry the same predictive value and impact in similar ways upon those being tested and thus warrant the same protections and safeguards. Whilst the requirement for counselling before and after the test is undoubtedly justified where the result of the genetic test will indicate a risk of serious inherited disease in the patient or a family member, it might be disproportionate to require the same standards for other types of genetic tests: an example might be some susceptibility tests or drug response tests, where the results are not as predictive or the potential results so significant.

A major concern is that, in combination, these amendments will reduce access to clinically useful genetic tests and hinder the mainstreaming of beneficial technologies into other clinical areas.

Legislative process

The legislative process for European legislation requires draft text to be adopted by the European Parliament, debated by the Council of Europe (www.coe.int/en), and a final position agreed between the Council, European Parliament and the European Commission – the 'trilogue' process. The current draft of the *In Vitro* Diagnostic Medical Devices Regulation was formally adopted by the European Parliament in April 2014, and is currently being considered by the Council of Europe (in its Employment, Social Policy, Health and Consumer Affairs configuration). The outcome remains uncertain as many issues are contested, but the best estimates suggest that the process will be completed by mid-2016.

Joint statement

The PHG Foundation has been working with the Wellcome Trust (www.wellcome.ac.uk) to highlight these concerns, and the resultant joint statement has the support of many professional organisations, patient groups and pan-European bodies, including the BSGM. Over the next few months we will work with stakeholders and those involved in the legislative process to highlight the potential adverse impact of the new legislation. Our aim is to try to ensure that the legislators understand the significant burdens associated with what is proposed, and that the final version of the legislation does not unnecessarily or disproportionally restrict access to genetic testing technologies and that it reflects current clinical practice.

EU reforms put access to genetic testing in danger *cont…*

To find out more please contact Alison Hall (www.phgfoundation.org/contact/alison_hall/)

For further information on the *In Vitro* Diagnostic Medical Devices Regulation: (http://eur-lex.europa.eu/legal-content/EN/HIS/?uri=CELEX:52012PC0541&qid=1429543752957)

To access the Joint statement: www.phgfoundation.org/file/16668/

Exploring how professionals make decisions to provide childhood sickle cell carrier testing

Melissa Noke

School of Psychological Sciences, University of Manchester

It is recommended by European guidelines (for example from the British Society for Human Genetics (BSHG) and European Society of Human Genetics (ESHG)) that, unless there are clear benefits of autosomal recessive carrier testing in childhood, it should be deferred to protect children's autonomous decision making. Despite this guidance, anecdotal evidence suggests that children in the United Kingdom receive carrier testing for sickle cell (SC).[1] Although generally regarded as clinically benign, there are contentious medical complications associated with SC carrier status (e.g. muscle breakdown due to extreme exercise).[2] To date, it has been unclear how or why professionals make decisions to provide tests. To explore the decision making process, interviews were carried out by researchers from the University of Manchester with twenty-five health care professionals in eight regions of England and one region of Scotland. The sample included heamoglobinopathy counsellors/nurses, health visitors/newborn screeners, a GP, Heamatologist, and Genetic Counsellor. Professionals were asked to discuss their experiences of advising about, or undertaking, childhood SC carrier testing.

Results highlighted that although 48% of professionals had received some form of counselling training (e.g. Professionals Education for Genetic Assessment and Screening; PEGASUS), only two were aware of, and used, carrier testing guidelines to inform their decisions about testing. Instead, professionals' advice was largely influenced by their personal beliefs about the importance of testing. Many professionals thought SC carrier status had health implications (e.g. oxygen difficulties during anaesthesia) which warranted early testing and these professionals consequently advised parents to undertake testing. Some working in Sickle Cell and Thalassaemia services also felt a sense of responsibility to provide testing to children within their 'cradle to grave' linked newborn and antenatal screening service. By contrast, others thought testing was unnecessary. These professionals discouraged testing when they assumed medical risks were minimal and children's autonomy should be preserved.

Some professionals, who believed testing should be provided, 'strongly encouraged' parents to have their children tested. Many parents reportedly agreed. However, conflict emerged when parents wished to receive testing 'just…to find out', but professionals discouraged this. Although professionals used various techniques to dissuade parents, some felt parents had the fundamental right to receive testing and if this was declined, it would be sought and received elsewhere. There were concerns that testing which was received by professionals (such as GPs) who were thought to lack the expertise to explain the results could cause misunderstandings.

Although testing was often influenced by the professional-parent discussion, children's autonomous wishes and professionals' capacity to provide tests also influenced the outcome.

Exploring how professionals make decisions to provide childhood sickle cell carrier testing *cont…*

Few professionals described talking to children about testing, however when consulted, younger children usually declined, but older children demonstrated interest. Most tests were not undertaken when children refused. Despite advising about testing, professionals did not always have the capability to test children within their role - some could not personally undertake these, but could authorise them at the hospital or GP service. When disagreements about testing a child occurred between professionals, few reported making collaborative decisions and the more senior professional determined if tests were provided.

The results from this study highlight the importance of improved awareness of childhood carrier testing guidelines to support informed decision making which is based on consideration of the benefits and harms of testing in individual circumstances. This might require further evidence about the psychosocial impact of testing during childhood and medical implications of a SC carrier status. Guidance about how to interpret the clinical risks and whether these justify childhood testing may be particularly useful. Professionals who are aware of guidelines might also find it easier to advocate children's autonomous rights and discourage testing when faced with persistent parents. Training on strategies to engage children in discussions about testing when they have sufficient cognitive maturity could prove useful.

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1. Kai, J., Ulph, F., Cullinan. T, & Qureshi, N. (2009). *Health Technology Assessment, 13*(57), 1–82. doi: 10.3310/hta13570.
2. Tsaras, G., Owusu-Ansah, A., Boateng, F. O., & Amoateng-Adjepong, Y. (2009). *The American Journal of Medicine, 122*(6), 507-512. doi: 10.1016/j.amjmed.2008.12.020.

The full article can be found in the European Journal of Human Genetics:
Noke, M., Peters, S., Wearden, A. & Ulph, F. (2015). *European Journal of Human Genetics*, 1-7. doi:10.1038/ejhg.2015.104

For further information about the study or the full text article, please contact Dr Melissa Noke (melissa.noke@manchester.ac.uk).

Indo-UK Genetic Education Forum- The 2015 Round

Dhavendra Kumar

Institute of Medical Genetics University Hospital of Wales

The Indo-UK Genetic Education Forum, hosted by the Wales Gene Park, is a voluntary professional group founded and led by Professor Dhavendra Kumar, Consultant in Clinical Genetics, University Hospital of Wales, Cardiff, UK.

Since 2010, the forum has organised an annual series of seminars, workshops and symposia across the Indian subcontinent (see Table 1). The forum has established itself as one of the leading international organisations dedicated to promoting and raising awareness of genetic and genomic centric healthcare in India and neighbouring developing countries. For two successive years the Wellcome Trust UK has provided a small grant to cover overseas travel. Both the 2013 and 2014 rounds of seminars were accredited by the Royal Colleges of Physicians CPD programme. The Government of India, local public and private agencies in India sponsored costs incurred in conference venues, domestic travel and accommodation.

The 2015 Round of Seminars and Symposia

The 2015 round (29 January to 15 Feb 2015) was participated by a Faculty of 10 experts from UK, The Netherlands and Spain along with several clinicians and genetic experts from India. The faculty included Professor Dhavendra Kumar (Cardiff, Lead), Professor Mary Porteous (Edinburgh), Professor Andrew Read (Manchester), Dr Alan Fryer (Liverpool), Professor Perry Elliott (UCLH, London), Dr Pier Lambiase (UCLH, London), Dr Mieke val Haelst (Uttrecht, NL), Dr Paul van Haelst (Sneek, NL) and Dr Lorenzo Monstratt (A-Coruna, Spain).

Indo-UK Genetic Education Forum *cont…*

The programme was largely focussed on genetics and genomics in clinical medicine with particular reference to cardiovascular disorders. The symposiums collectively attracted 22 hours of CPD credits from the Royal College of Physicians, London. The Faculty travelled to the Post Graduate Institute of Medical Education and Research, Chandigarh; Himalayan Institute of Medical Sciences and Hemwati Nandan Bahuguna Medical University, Dehradun and King George's Medical University, Lucknow. In total around 1000 participants took part including senior and junior medical practitioners, resident trainee doctors, medical students, research scientists and laboratory personnel. Feedback has been consistently excellent with encouraging comments from wide ranging audience. The Forum has been invited by at least three leading Indian academic institutions to host similar programme in 2016.

1. Current Trends in Genetics of Heart Failure and Cardiac Arrhythmias

30 Jan-1 Feb 2015, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

Overseas faculty- Professor Dhavendra Kumar (Cardiff), Professor Perry Elliott (London), Professor Mary Porteous (Edinburgh), Professor Andrew Read (Manchester), Dr Alan Fryer (Liverpool), Dr Pier Lambiase (London), Dr Mieke van Haelst (Uttrecht), Dr Lorenza Monstraat (A-Coruna, Spain) and Dr. Paul van Haelst (Sneek, Holland)

This two day conference focussed on a number of inherited cardiovascular conditions encountered in clinical cardiology, emergency medicine and clinical genetics practice. Apart from the visiting overseas Faculty a number of distinguished cardiologists and cardiovascular scientists delivered the programme (See Figure 1). An account of the prevalence and challenges of inherited heart and blood disorders in India was provided by Professor KK Talwar, (Professor of Cardiology, Former Director PGI, Chandigarh and Director of Max Heart Hospital, New Delhi). The highlight of the conference was plenary lecture on *Clinical Cardiology in the Genome Era* delivered by Professor Perry Elliott, The Heart Hospital, UCL, London, UK (See Figure 2).

Figure 1 (Left): Professor Kumar with Professor Talwar (next on left) Inaugurating the Cardiac Genetics Symposium in PGIMER, Chandigarh, India.

Figure 2: Professor Elliott (UCLH) delivering the Key Note Lecture in PGIMER, Chandigarh, India.

2. The genetic and genomic practice of clinical medicine and cardiology

3 Feb 2015, Himalayan Institute of Medical Sciences, Dehradun, Uttarakhand, India.

Overseas faculty- Professor Dhavendra Kumar (Cardiff), Professor Perry Elliott (London), Professor Mary Porteous (Edinburgh), Professor Andrew Read (Manchester), Dr Alan Fryer (Liverpool), Dr Pier Lambiase (London), Dr Mieke van Haelst (Uttrecht), Dr Lorenza Monstraat (A-Coruna, Spain) and Dr Paul van Haelst (Sneek, Holland)

This one day high profile scientific symposium focused on rapidly evolving and emerging applications of genetics and genomics in the current and future practice of Clinical Medicine (See Figure 3, and 4). A team of international genetic & genomic practitioners and scientists presented key topics with real time examples providing a clear landscape for the benefit of junior and senior secondary and tertiary medical practitioners of India. The seminar was approved by the Royal College of Physicians (London) for continued medical education & professional development.

Figure 3: Professor Anita Sharma, Head of Medicine, Himalayan Institute of Medical Sciences, Chief Convenor of the Conference

Table 1: List of seminars and conferences organised by the Forum 2010-2014

Seminar/Conference	Date and Place	Overseas Faculty
Short course on clinical cardiovascular genetics	30-31 January 2010; Bangalore, India	Professor Dhavendra Kumar (Cardiff), Dr Perry Elliott (London), Dr Bronwyn Kerr (Manchester) and Dr Rob Hastings (Bristol and Oxford).
Current trends in Clinical Genetics & Genomic Medicine	21-24 March 2011; Chettinad Health City, Chennai, India	Professor Dhavendra Kumar (Cardiff), Professor Frances Flinter (London), Dr Leema Roberts (London) and Dr Robert Elles (Manchester)
Current practice of genetic and genomic medicine	26-27 March; Apollo Hospital, New Delhi, India	Professor Dhavendra Kumar (Cardiff), Professor Frances Flinter (London) and Dr Robert Elles (Manchester)
Genes and Human Malformations- Indian Birth Defects Conference	27-29 February 2012; Bangalore, India; part of the Indo-UK Genetic Education Forum, jointly supported by CGS/BSHG and hosted by the Centre for Human Genetics, Indian Institute of Science, Bangalore, India	Professor Dhavendra Kumar (Cardiff), Professor Jill Clayton-Smith (Manchester), Professor. Ruth Newbury-Ecob (Bristol), Dr Andrew Jackson (Edinburgh) and Dr Peter Turnpenny (Exeter)
The First Indian Cancer Genetics Conference	23-25 January 2013, Advanced Center for Treatment, Research and Education for Cancer (ACTREC), Tata Memorial Cancer Trust, Mumbai, India; jointly organised by the Indo-UK Genetic Education Forum and ACTREC.	Professor Shirley Hodgson (London), Professor Eamon Maher (Birmingham/Cambridge), Professor Gareth Evans (Manchester). Professor Diana Eccles (Southampton), Professor Meena Upadhyaya (Cardiff) and Professor Dhavendra Kumar (Cardiff)
The Next Revolution of Genetics and Genomics	27-29 January 2013; Postgraduate Education Centre, Ram Manohar Lohia Hospital, New Delhi; jointly organised by the Indo-UK Genetic Education Forum with the Indian Academy of Medical Genetics and the Centre for Genetic Medicine, Sir Ganga Ram Hospital, New Delhi, India.	Professor Shirley Hodgson (London), Professor Eamon Maher (Birmingham/Cambridge), Professor Gareth Evans (Manchester). Professor Diana Eccles (Southampton), Professor Meena Upadhyaya (Cardiff), Professor Sian Ellard (Exeter), Dr Bert de Vries (Nijmegan) and Professor Dhavendra Kumar (Cardiff)
Current Trends in Genetic and Genomic medicine	31 January 2013; Dr Ram Manohar Lohia Post Graduate Institute of Medical Sciences, Gomti Nagar, Lucknow; jointly organised by the Indo-UK Genetic Education Forum	Professor Shirley Hodgson (London), Professor Meena Upadhyaya (Cardiff), Professor Sian Ellard (Exeter), Dr Bert de Vries (NIjmegan) and Professor Dhavendra Kumar (Cardiff)
Gains of Genomic Research for Medicine and Biology	4 February 2013; The Ranbaxy Science Foundation Symposium, Institute of Immunology, New Delhi, India.	Professor Dhavendra Kumar (Cardiff)
International Birth Defects Conference	9-11 February 2014; Jointly organised on behalf of the Indo UK Genetic Education Forum, Wales Gene Park and the Human Genetics Unit, The University of Colombo, Sri Lanka	Professor Dhavendra Kumar (Cardiff), Professor Philip Beales (London), Professor Daniela Pilz (Cardiff), Dr Sarah Smithson (Bristol)and Dr Trevor Cole (Birmingham)
Ophthalmic Genetics Seminar	11 February 2014; Jointly organised on behalf of the Indo UK Genetic Education Forum, Wales Gene Park and the Human Genetics Unit, The University of Colombo, Sri Lanka.	Professor Graeme Black (Manchester), Professor Veronica van Heyningon (Edinburgh/London), Dr Trevor Cole (Birmingham), Dr Georgina Hall (Manchester) and Professor Dhavendra Kumar (Cardiff)
Indian Ophthalmic Genetics Conference	15-16 February 2014; Jointly organised on behalf of the Indo UK Genetic Education Forum, Wales Gene Park and Narayana Nethralaya, Bangalore. India.	Professor Graeme Black (Manchester), Professor Veronica van Heyningon (Edinburgh/London), Dr Georgina Hall (Manchester), Dr Trevor Cole (Birmingham), Professor Daniela Pilz (Cardiff) and Professor Dhavendra Kumar (Cardiff)
Genes and Genome	21 Feb 2014; Organised by the Dept. of Human Genetics, Guru Nanak Dev University, Amritsar, Punjab, India.	Professor Dhavendra Kumar (Cardiff)

Indo-UK Genetic Education Forum *cont…*

Figure 4: Dr Lorenzo Monstraat, Consultant Cardiologist/ Cardiac Genetics from Spain at the Genomic Medicine Symposium in Sahu Ram Health University, Dehradun, India.

3. **Our genes and genomes in Health and Disease**, 4 February 2015, Open seminar hosted by Hemwati Nandan Bahuguna Medical University, Dehradun;held in the Indian Council for Forest Research and Education.

One day seminar aimed at young secondary and graduate science students provided basic introduction to genetics and genomics with its wide ranging applications. The seminar was attended by around 300 high school and university students from local and nearby science schools and colleges (See Figure 5).

Figure 5: Professor Andrew Read delivering Public Lecture in Dehradun at the 'Our Genes & Genomes' Open Seminar

4. **Genetics and Genomics in Modern Clinical Medicine**
9-10 Feb 2015, King George's Medical University, Lucknow, UP, India.

Overseas faculty- Professor Dhavendra Kumar (Cardiff), Professor Mary Porteous (Edinburgh), Professor Andrew Read (Manchester), Dr Alan Fryer (Liverpool)

The two day symposium in the historic city of Lucknow provided the audience and participants clinically oriented introduction to genetics and genomics. Local researchers and postgraduates presented their research as posters. The visiting Faculty went through all posters and the best two were given prizes sponsored by the Research Cell of the King George's Medical University.

Figure 7 (right): The UK Faculty visiting KGMU Campus- from right Professor Read, Professor Porteous, Professor Ravi Kant (VC, KGMU), Dr Alan Fryer, Professor Kumar and Professor Khan (Dental Faculty).

Figure 6 (left):The Faculty of the Genetic and Genomic Medicine Conference, from left Professor Mary Porteous, Dr Alan Fryer, Professor Andrew Read, Professor Dhavendra Kumar, Professor Ravi Kant (VC, KGMU), Professor Ravinder Garg (Research Dean, KGMU) and Professor Mahboob Khan (Dean-Dental Faculty, KGMU)

Figure 8: The UK visitors in the historic KGMU Campus- from left Dhavendra Kumar, Alan Fryer, Mary Porteous and Andrew Read.

In addition to the above engagements, Professor Dhavendra Kumar, Dr. Alan Fryer and Dr. Peter Turnpenny (Exeter) participated as invited Faculty to the Second National Paediatric Genetics Conference, held on 13-15 February in the Dinanath Mangeshkar Hospital Medical School & Research Centre in Pune, Maharashtra, India. Professor Dhavendra Kumar visited Chennai, Tamil Nadu as the Visiting Professor to the Chettinad Academy for Research and Education of the Chettinad Health University. All events and seminars were highly successful with excellent feedback from Indian colleagues and participants.

The Forum is invited to organise future genetic and genomic educational and research events in 2016. The highlight for the 2016 round will be the *Third Biennial International Birth Defects Conference* in New Delhi jointly convened by the Forum with the Indian Academy of Medical Genetics. Anyone interested to join the Faculty and/or leading a particular seminar is invited to contact Professor Dhavendra Kumar for informal discussion and further information.

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An update on national recruitment in the Newborn X linked Hypohidrotic Ectodermal Dysplasia (XLHED) Clinical Trial.

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Institute of Medical Genetics, Cardiff

Background

X-linked Hypohidrotic Ectodermal Dysplasia (XLHED) is a condition that affects epithelial/mesenchymal interaction with involvement of the ectoderm and the endoderm. It results from an alteration in the Ectodysplasin A (*EDA*) gene, on the X chromosome. The EDA Receptor (EDAR) binds specifically the A1 isoform of EDA (EDA-A1) for signal transmission.[1]

Affected males characteristically present with hypotrichosis, oligodontia, and hypohidrosis. The symptoms include an increased susceptibility to hyperthermia and respiratory infections, chronic skin problems, and psychological issues arising from the distinctive appearance of affected males.[2]

A phase two, open-label trial is currently underway, to assess the safety, pharmacokinetics and immunogenicity of the postnatal administration of EDI200. This is a fully humanized EDA-A1 replacement molecule, linked to a human IgG/Fc sequence (See Figure 1). Male infants, recruited between 48 hours and 14 days of age, with a genetically confirmed diagnosis of XLHED, are eligible to receive five doses over 14 days.

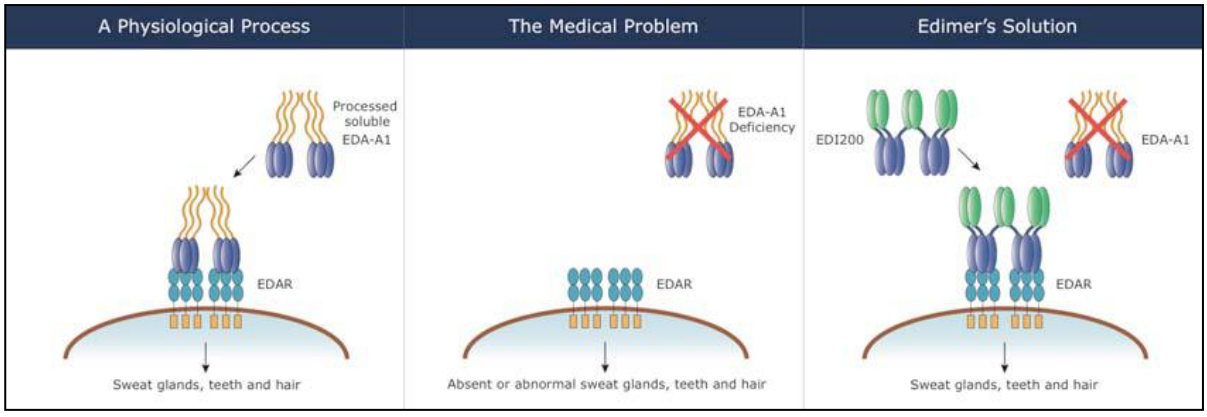


Figure 1: Mode of action of EDI 200

Globally, the aim is to recruit 12 XLHED affected neonates. Cardiff is participating as a European recruitment centre, along with three other centres in Germany, France and Italy. Here we report on the local experience of recruiting and treating two neonatal patients, one from Ireland and one from England.

Local Experience

Both at-risk males (individuals A and D in Figure 2) were identified antenatally, following confirmation of maternal carrier status, conferring 50% risk. Antenatal ultrasound scans giving accurate picture of dental development were undertaken in the third trimester in both families, helping parents to prepare for recruitment to the study. Genetic diagnosis was obtained using umbilical cord blood, which was delivered by courier to the laboratory at the Cardiff Institute of Medical Genetics for analysis.

Following genetic confirmation of the diagnosis, the infants were admitted to the Children's Hospital for Wales at about one week of age for a 21-day period

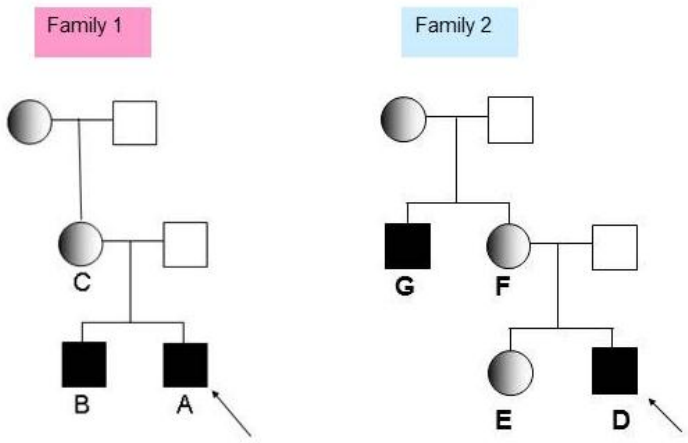
XLHED Clinical Trial *cont…*

The treatment was administered in five doses. Blood and urine tests to monitor the safety of the treatment (including FBC, LFT, U+E, Glucose and urine microscopy), were taken on treatment days 1 (TD1) and 15 (with TD0 being the day of the first dose). Immunogenicity and pharmacokinetics were measured after the first and final doses. Skin biopsies were taken prior to the first dose and after the first and last treatments (See Figure 3).

Clinical review including ophthalmology, dermatology and neurodevelopmental assessments was undertaken. Vivascope ultra-high resolution photography of the skin was taken prior to the first day of treatment to determine sweat gland density (see Figure 4).

Outcome measures

There were no clinically or biochemically apparent complications from the treatment in either patient during their admission to the Children's Hospital for Wales.Patient A from family 1 is currently participating in the extension study (annual assessments from 1-10 years) and Patient D from family 2 is still in the main study, having assessments over the period of treatment and then at two, four and six months.



A	Recruited patient from family 1
B	Proband from family 1 – severely affected with typical facies, conical teeth Mutation: Hemizygous for *EDA c.467G>A*
C	Carrier female, some facial features noted
D	Recruited patient from family 2 – no sweat glands present on vivascope, absent deciduous dentition, dry skin, typical facies
E	Carrier female, some facial features noted
F	Carrier female, some facial features noted
G	Proband from family 2, severely affected. Significant immune compromise with recurrent admissions for LRTI throughout life Mutation: Hemizygous for *EDA c.1049G>T, in exon 9*

Figure 2 – Pedigrees and details for Family 1 and 2

This trial required careful co-ordination of paediatrics, dermatology, genetics and special biochemistry to ensure that samples were taken and delivered at specific and exact times after each dose. The follow up study requires input from neonatology to perform the required developmental assessments and ophthalmology to assess corneal problems and meibomian gland development (these glands are in the eye lids and secrete the oily barrier that prevents the corneal surface from drying). The patients also require jaw radiographs to assess dentition and medical photography to document any facial features present.

Further potential patients have been identified, through pregnant females having known affected male family members. Antenatally, ultrasound assessment of the fetal jaw for the presence of the tooth buds is being undertaken to provide families with further information prior to delivery. We hope to recruit more patients in the coming months.

Future developments

In utero administration of the preparation, transplacentally, via the mother's circulatory system, or directly intrauterine in animal models have shown promising outcomes.[3]

Human ectodermal tissue development is initiated during the embryonic period and morphogenesis does continue postnatally.[4] Therefore, the next logical step which may be more effective at ameliorating the effects of this condition would be to attempt prenatal therapy if there are no apparent ill effects of the treatment in human neonates.

XLHED Clinical Trial *cont…*

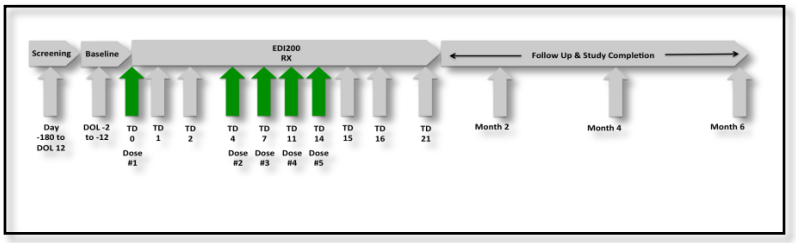


Figure 3: Treatment and investigation protocol for EDI200 safety trial

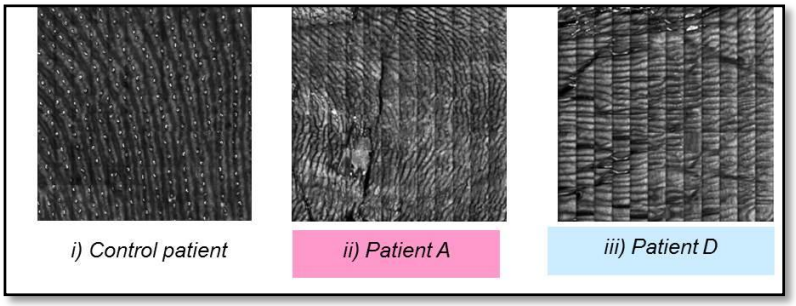


Figure 4: Vivascope pictures demonstrating absence of sweat glands (ii and iii) compared to a control patient (i)

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2. Clarke A, Phillips DI, Brown R and Harper PS. 1987. Archives of Disease in Childhood 62: 989-996

3. Gaide O and Schneider P. 2003. Nature Medicine 9 (5): 614-618

4 Pispa J and Thesleff I. 2003. Developmental Biology 262 (2): 195-205

Acknowledgements

Mr Ramsey Johnson, Senior Director, Clinical and Regulatory Operations, Edimer Pharmaceuticals

Noticeboard

Forthcoming events

Cancer Genetics Group: 4 December 2015

Venue: Institute of Neurology, Queen's Square, London UK
Contact: lucy.side@gosh.nhs.uk
Website: bsgm.org.uk

UK-Dutch Joint Clinical Genetics and Cancer Genetics Conference: 7-8 March 2016

Venue: City Hall, Cardiff, Wales, UK
Contact: dhavendra.kumar@wales.nhs.uk
Website: www.bsgm.org.uk

The International Congress of Human Genetics: 3-7 April 2016

Venue: Kyoto International Conference Centre, Japan
Contact: ichg2016@congre.co.jp
Website: www.ichg2016.org

Association of Genetic Nurses and Counsellors: 26-27 April 2016

Venue: Liverpool, UK
Contact: lisa.mcgrath@lwh.nhs.uk; louise.dubois@lwh.nhs.uk; pam.harris@lwh.nhs.uk; janet.birch@lwh.nhs.uk
Website: www.bsgm.org.uk

The European Human Genetic Conference: 21-24 May 2016

Venue: Barcelona, Spain
Website: www.eshg.org

British Society for Genetic Medicine Conference: 22 September 2016

Venue: London, UK
Contact: bshg@bshg.org.uk
Website: www.bsgm.org.uk

The American Society of Human Genetics: 18-22 October 2016

Venue: Vancouver, Canada
Website: www.ashg.org

Noticeboard

Welcome New Members

Isa Abdi Rad	CGS
Fatima Ali	CGS
Angel Alonso-Sanchez	CGS
Jose Antonio Aragon-Martin	ACGS
Mohammad Atheab	ACGS
Julia Baptista	ACGS
Marta Bertoli	CGS
Ramsay Bowden	CGS
Kimberley Bradbury	CGS
Alysha Bray	BSGM
Jonathan Bruty	Lab trainee
Laura Butland	AGNC
Vera Cerqueira	Lab trainee
Heather Chalinor	AGNC
Audrey Dearing	AGNC
Cristina Dias	CGS
Andrea Djolovic	AGNC
Laura Dutton	ACGS
Sarah Everest	AGNC
Jennifer Fairley	ACGS
Amy Goldman	AGNC
Risha Govind	CGS
Harriet Hewitt	ACGS
Rachel Irving	BSGM
Samah Jassam	ACGS
Jessica Jones	Lab trainee
Julie McMahon	ACGS
Kirsten Patterson	AGNC
Evgenia Petrides	Lab trainee
Caroline Picard	CGS
Corrina Powell	CGS
Rebecca Reamonn	BSGM
Claire Salter	CGS
Elizabeth Scully	AGNC
Anna Skowronska	BSGM
Alison Stevens	ACGS
G. Jawahar Swaminathan	BSGM
Ian Tully	CGS
Lorraine Warne	ACGS
Catriona Whyte	AGNC
Martin Widschwendter	BSGM

2015 Galton Institute Conference – Mate Choice

Wednesday 11 November at The Royal Society, London.

Speakers will explore the genetic, biological and anthropological consequences of mate selection in human societies. Professor Alan Bittles from the Centre for Comparative Genomics at Murdoch University in Perth, Western Australia will be giving The Galton Lecture on Patterns of consanguineous marriage across the world and their consequences.

Entrance is strictly by ticket, available from the General Secretary: betty.nixon@talk21.com. Attendance is free, with a £10 contribution to refreshments. For further information see www.galtoninstitute.org.uk

BSGM News Editor

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Editorial

Martin Schwarz

Dear friends and colleagues! This might be an unusual way to begin an editorial but since this is by way of being my *valete*, I crave the indulgence of the Editor-in-Chief and hope you will forgive the departure from the customary third person narrative required by the Editors' Style Guide. Yes, Dear Readers, this is my swan-song, as I pass over the reins to Emma Huxley, who is more than capable of looking after the shop.

I have recently been engaged in the final stages of de-cluttering my work-related paperwork, sorting into recyclable (90%), shreddable (9%), and 'keepable' (1%). Some stuff is just hard to consign to the bonfire or landfill, including personal letters from the likes of Lap-Chee Tsui, Jean-Jacques Cassiman and other luminaries. I also have my Royal College of Pathologists Diploma in Clinical Cytogenetics, to remind me of a previous existence in which I passed my days staring down a microscope at those peculiar stripy chromosomes! [I came over from the Dark Side in the early 80s when I discovered the joys of extracting DNA]. Other items I still feel unable to dispose of include the Hybond membranes [look it up, young people!] on which we discovered DeltaI507 (the second CF mutation to be recorded) in the autumn of 1989 (so they're no longer radioactive!).

Apart from the paper records, a great chunk of my post-1995 correspondence disappeared in one fell swoop when my hospital and nhs.net email accounts mysteriously fell off the radar. I think it was some Higher Power telling me it was time to hang up my editor's proof-marking red pencil (it being already some time since I hung up my nitrile gloves and Gilson pipettes!).

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So it's time to say goodbye and thank all the contributors, past and present, for their most welcome and erudite submissions to this august journal. It has been both a pleasure and an education to compile each issue. Please continue to send your articles in; they can be short or long(ish) and relate to any topic pertaining to our profession. They are particularly welcome when they are accompanied by illustrations or photographs, even if the subject matter is 'a group of EMQN Fragile X Assessors enjoying a local hostelry'!

Finally, as this is my last editorial, I would like to take this opportunity to thank all those who have worked with me over the years – scientists, technologists, clinicians and academics – without whose help my time in molecular genetics (and, indeed, cytogenetics) would not have been anywhere near as rewarding or as much fun. Heartfelt thanks to all of you.

Now I'm off to mow the lawn

Improved fixation and additional washing improves consistency of FISH following immunomagnetic cell separation in myeloma.

Nick Telford[1] and Sheila JM O'Connor [2]

[1]Oncology Cytogenetics Service, The Christie Pathology Partnership, The Christie NHS Foundation Trust
[2] Haematological Malignancy Diagnostic Service, St James's Institute of Oncology

Fluorescence *in situ* hybridization (FISH) studies are recommended in all myeloma patients at diagnosis[1] and this should be combined with a method of plasma cell enrichment or selection.[2] .An increasingly popular approach for cell enrichment is immunomagnetic separation of CD138 positive cells due to the simplicity and relatively low cost of some commercial methods. This approach can also be used to select for different cell surface markers in other disease situations.

The laboratories at HMDS Leeds and Oncology Cytogenetics at The Christie occasionally receive the same bone marrow (BM) aspirate samples for a different range of tests as part of diagnostic work-up. This permits the laboratories to retest each other's samples with borderline and unusual results. This has resulted in the detection of a small number of discordant results for TP53 deletion with FISH assays on immunomagnetic selected cells. The discrepancy appears as a false positive result for TP53 deletion (>20% cells deleted) followed by a normal result obtained in duplicate or when retested within the same laboratory. Although our experience relates to CD138+ selection to enrich for plasma cells, we are concerned that this could occur with any combination of immunomagnetic and FISH testing assays.

This problem is subtle – we have independently noted 'patchy' hybridisation with random signal loss in individual cells, in otherwise good quality FISH with satisfactory controls. This appears to affect all FISH probes from a variety of manufacturers. Initially this was thought to reflect pre-analytical variables or sample problems. Myeloma samples are frequently of poor quality and we know that the cytogenetics can be complex with unbalanced abnormalities occurring frequently. This complication of sample variability with the expectation of heterogeneous signal patterns has made this problem difficult to identify. The observation that repeat testing a few days or weeks later results in even hybridisation and in some cases normalisation of a previously apparently deleted TP53 result has led our laboratories to perform an extensive review of TP53 FISH carried out after CD138+ plasma cell enrichment.

Patchy hybridisation appears to be related to the use of immunomagnetic plasma cell selection; this is not a feature of any other FISH on unselected cells. The Christie and HMDS Leeds use different kits/processes for plasma cell enrichment and whilst both laboratories use FISH probes from the same company, other manufacturers' reagents have been used previously and we do not believe that the problem is related to use of a specific probe. There is no other common reagent or factor identified to date.

Peculiarities of plasma cells and their selection might combine to inhibit FISH in an unusual way. When the cells have been processed, the cell membrane is coated with iron oxide particles linked to the monoclonal antibody. The process is gentle and designed not to activate cells or damage them for downstream investigations, so over the course of a few hours the beads appear to be shed from the cell surface. Those shed iron oxide beads could stay in the suspension unless adequately washed away prior to slide-making. Furthermore, plasma cells are actively antibody-producing and will have abundant protein and RNA in their cytoplasm. It may be that plasma cells take considerably longer to fully fix compared to other cells, compounded by their being coated with monoclonal antibody attached to magnetic beads.

We suggest that a hypothesis for the cause of signal loss in these preparations is interference of hybridisation and inadequate fixation. Both departments have made a small change in their protocols to increase storage in methanol-acetic acid fixative for four to seven days prior to preparing the slides for FISH. The fixative is replaced before FISH set-up. Additional washes following the selection process but before fixation resulted in improved hybridisation also but caused dramatic loss of cells, so this small compromise of increasing the overall fixation time appears satisfactory. FISH set-up remains unchanged and

Improved fixation and additional washing improves consistency of FISH following immunomagnetic cell separation in myeloma cont…

the probe manufacturer's protocol is followed. Since implementing these simple changes there has been an improvement to the overall quality of hybridisation.

We are reporting these findings as we are concerned that they might not be unique to our laboratories and present a risk of false positive test results. The original results looked very convincing and only repeat testing of samples with a different outcome alerted us to the problem. Variable signal patterns in a case, including cells with loss of both test signals and/or loss of a control signal (e.g. 0R2G, 1R1G etc.) as well as the conventional 1R2G 'deleted' pattern, could indicate this feature. We are suspicious of deleted cell populations of low or mid-level size (20~50%) which appear to be those of most risk. In well-enriched cell populations, a small proportion of deleted cells might represent evolution of a sideline with TP53 deletion and the emergence of a real clone but perhaps this phenomenon is not as common as we think.

We recommend that departments using immunomagnetic cell selection methods prior to FISH testing review their methodology and its validation

for purpose and also consider an audit of suspicious TP53 deleted results. Even though patchy hybridisation appears to be sample related, the interpretation of FISH for 'breakapart' or 'dual fusion' probes is more robust and the consequences of failure to unmask the target DNA is only a practical concern for deletion probe sets. We would be interested to hear of other laboratories' experience of TP53 deletion by FISH on immunomagnetic selected cells.

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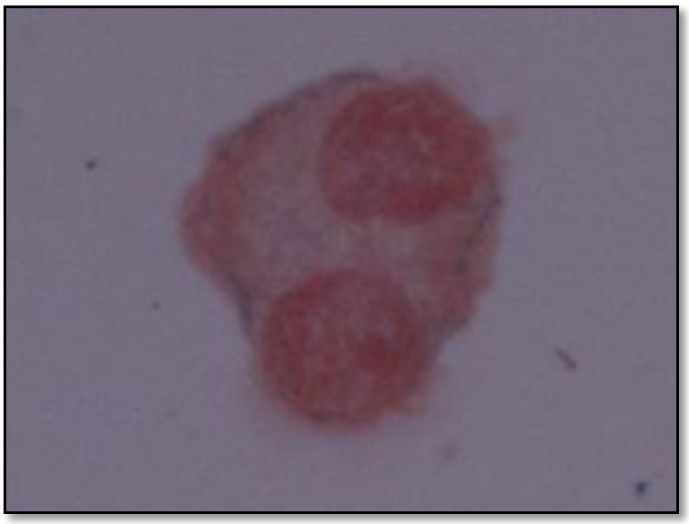

Figure 1: Perls stain on a plasma cell (MAA fixed) – there is cell surface membrane staining (blue) indicating the presence of iron on the cell

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2. Ross et al (2012) Haematologica 97: 1272-1277

Feedback of the FRCPath Part 1 examinations in Genetics, Clinical Cytogenetics and Molecular Genetics 2015.

Graham Fews[1], Tracy Lester[2], Sian Morgan[3] and Simon Ramsden[4]

[1]West Midlands Regional Genetics Laboratory, Birmingham Women's NHS Foundation Trust
[2]Oxford Medical Genetics Laboratories, Oxford University Hospitals NHS Trust
[3]Medical Genetics Services for Wales, University Hospital of Wales
[4]Manchester Centre for Genomic Medicine, Central Manchester University Hospitals Foundation Trust.

There were a total of 20 candidates who sat the Part 1 FRCPath written papers for genetics which were held Tuesday 24 March. For the first time this comprised of 3 disciplines; 9 candidates sat in Clinical Cytogenetics, 8 sat in Molecular Genetics and 3 sat the new Genetics examination. The pass rates were 55.6% for Clinical Cytogenetics, 87.5% for Molecular Genetics and 100% for Genetics. Once again the examination consisted of a morning essay paper 1 and an afternoon short answer question (SAQ) paper 2.

The SAQ paper consisted of 20 questions containing a stem question and 6 sub-questions worth a total of 20 marks. This year 10 SAQ questions were common across the three examinations, with the remaining 10 questions within the Genetics examination taken from the Clinical Cytogenetics and Molecular Genetics papers. Most candidates provided an answer for all questions however candidates are reminded that on average each question should take no longer than 9 minutes to complete. In general the unsuccessful candidates scored lower on the SAQ paper than their peers.

The essay paper was shared across all examinations and required answers to 4 out of the 5 questions set.

Question 1

What are the drivers towards integration of pathology genetic services? What are the opportunities and challenges posed by this model?

This question was answered by 7 candidates sitting the cytogenetics exam, 7 candidates sitting the molecular genetics exam and 1 candidate sitting the genetics exam. Examiners were looking for a description of tests across pathology services (not just molecular and cytogenetics) that could benefit from integration, as well as examples of the drivers for change (such as new technologies, financial pressures). At least one opportunity and challenge should have been described. The most common problems in failed essays were insufficient detail and failure to answer all parts of the question.

Question 2

A sample sent in for genetic testing has been identified via analysis to be of a different gender than that reported on the referral card. Describe the procedure you would follow to investigate this, giving both scientific and technical reasons that could explain the discrepancy, considering both molecular and cytogenetic causes.

This question was answered by 5 candidates sitting the cytogenetics exam, 5 candidates sitting the molecular genetics exam and all candidates sitting the genetics exam. Examiners were looking for a description of the root cause analysis and incident reporting process with at least one molecular and cytogenetic example of possible causes. Candidates who had difficulty with this question failed to demonstrate sufficient detail and clarity within the answer.

Question 3

Describe a comprehensive cost efficient testing strategy for developmental delay in children and adolescents. Describe the limitations of your chosen approach and why this strategy might change over the next 5 years.

This question was answered by 7 candidates sitting the cytogenetics exam, 6 candidates sitting the molecular genetics exam and all candidates sitting the genetics exam. Examiners were looking for a description of a testing strategy for developmental delay in children, with at least one limitation of the approach chosen and an explanation as to why or how that might change over the next

Feedback of the FRCPath Part 1 examinations cont…

5 years. A description of methodology with no specific strategy was insufficient. This question was answered well by the majority of candidates. Lack of awareness of future strategies and depth of knowledge were the main reasons for failure.

Question 4
What is the definition of stratified medicine? Use specific examples of conditions within cancer and non-cancer where cytogenetic and/or molecular genetic findings are clinically relevant to stratified medicine.
This question was answered by 8 candidates sitting the cytogenetics exam, 6 candidates sitting the molecular genetics exam and all candidates sitting the genetics exam. Examiners were looking for a description of stratified medicine, together with examples from both cancer and non-cancer conditions that illustrated the clinical use of molecular genetics in stratified medicine. This question was generally answered well. Those candidates who performed less well on this question failed to demonstrate a reasoned and detailed understanding.

Question 5
You are invited to contribute to a multi-disciplinary meeting to formulate an approach to deal with incidental findings. What are incidental findings, how do they arise, and why are they a problem? In your opinion what should the approach of genetic laboratories be with regard to incidental findings? Justify your answer using examples from both cytogenetic and molecular laboratories.
This question was answered by all candidates sitting the cytogenetics exam, all candidates sitting the molecular genetics exam and 2 candidates sitting the genetics exam. Examiners were looking for description of incidental findings, together with examples from both molecular and cytogenetics to show why they are a problem. Candidates were expected to give supportive arguments for their chosen approach. This question gave the fewest problems. Candidates who failed this question showed a lack of detailed understanding and reasoned implementation.

Those planning to sit FRCPath Part 1 examinations are reminded that the last sitting of the Clinical Cytogenetics and Molecular Genetics papers will be held in 2017. From 2018 all candidates will sit the Genetics examination.

The winners of the inaugural Academy for Healthcare Science Awards were announced at a glittering ceremony as part of the 2014 AHCS Congress.

The first annual AHCS awards were presented on the evening of Monday 8 December at a celebration dinner, during the Academy's inaugural two day Congress, *Passionate for patients, passionate about science*.

Professor Sian Ellard receives her Award from AHCS Chairman Sir Duncan Nichol

The objective of the awards is to recognise the active scientists who, day in and day out, make the most incredible contributions to knowledge, discovery, and medical advancement and make a real difference to people's lives, often in the least recognised way. The awards went to Professor Sian Ellard, and Sue Kenworthy.

Sian Ellard is a scientist who was nominated for her research work in neonatal diabetes. Her work is described as having transformed the lives of patients throughout the world. Together with her team at the Royal Devon & Exeter NHS FT and Peninsula Medical School, Sian has discovered 14 new causes of monogenic disease.

Their biggest breakthrough was finding KATP channel mutations that are the most common cause of neonatal diabetes, where transfer from insulin injections to sulphonylurea tablets results in blood glucose control. Those patients would previously have faced a lifetime of insulin therapy and the resulting risk of diabetic complications in later life.

Around 20% of those patients have a severe mutation which causes developmental delay that may be ameliorated through early treatment with sulphonylureas to improve KATP channel activity in the brain

Congratulations Sian!!

Genetics in New Zealand: An STP Elective

Jennie Dring,
West Midlands Regional Genetics Laboratory,
Birmingham Women's NHS Foundation Trust.

Electives are a valuable part of the Scientist Training Programme (STP) taking place at any point in training and lasting 4-6 weeks. The aim of the elective is to facilitate wider experience of healthcare and/or the practice of healthcare science in a cultural and/or clinical setting that is different from the usual training environment. In addition the elective provides opportunities to:

- Explore in depth areas beyond the scope of the scientist training programme
- Increase awareness of important health issues and develop an understanding of the effect of disease on communities and individuals in different cultural contexts
- Explore unfamiliar scientific, social, economic or cultural areas
- Become more proficient at communication with individuals from different social, cultural and ethical backgrounds
- Relate your experiences to you own area of practice.

The elective is led and planned by the trainee from generating initial ideas, setting learning outcomes, meeting objectives and finally feeding back to colleagues.

As a Genetics STP at the West Midlands Regional Genetics Laboratory, I decided I wanted to explore Genetics provision in a different part of the world so I spent 4 weeks working at the Wellington Regional Genetics Service (WRGS) in New Zealand for my elective.

New Zealand has a population of ~4.5 million (1 million less than my local region) and is slightly larger than the UK. Healthcare in New Zealand is partially public funded with some services free and others subsided, for instance there is a fee for every visit to a GP. In addition, residents pay a levy for comprehensive no-fault injury cover which provides for hospital care in the event of an accident. All Genetics services are provided free to the user if they are clinically appropriate.

WRGS is one of two major genetics services in the country with the small team serving a large proportion of the population including both cytogenetic and molecular testing. There are strong links with the co-located clinical genetics service and local haematology team.

The aims of my elective included identifying referral patterns and the structures utilised to respond to demand, comparing and contrasting how cultural differences affect practice and comparing the patient pathway for several common conditions from initial consultation to the reporting of results. Spending time with in all areas of the service provided me with the opportunity to observe the differences in practice between the two countries.

Some of the challenges faced in New Zealand are the large geographical spread of patients, the large number of tests that have to be sent away both to other New Zealand labs, Australia, the US or Europe and the small local workforce. Australasia best practice guidelines differ from those in the UK with shorter turnaround times for some testing though the Wellington laboratory has some of the best turnaround times in Australasia.

The elective has been a valuable experience, enabling holistic consideration of genetics in the wider healthcare environment and has contributed both to my own professional development and future practice.

I would like to thank both my department for supporting my elective and the team in Wellington for welcoming me and ensuring I got the most out of my time in New Zealand.

Healthcare Science Awards 2015 - Rising Star

Genomic Medicine was evident at the front line of Healthcare Science during the Healthcare Science: Making it Happen event 16-17 March 2015. The event encompassed the 2015 Healthcare Science Awards (#HCS15) at which Lowri Hughes, West Midlands Regional Genetics Laboratory, was announced winner of the Rinsing Star – Life Sciences category.

The citation for Lowri Hughes read:
"Lowri was one of the first STPs in Genetics starting her training in Birmingham in 2010. Her ability to work in a flexible and innovative way was exemplified by her continuing her Master's degree whilst on a 6 month period of maternity leave; she returned full time to complete her training. Her MSc project has facilitated development of a Next Generation Sequencing panel for disorders of sexual development.

On completion of her STP training Lowri relocated to Liverpool to work in the Merseyside and Cheshire Regional Molecular Genetics Laboratory; twelve months later Lowri returned to Birmingham to join the first cohort of HSSTs in Genetics.

Throughout her training Lowri has been proactive in representing trainees and was selected as Trainee representative on the Healthcare Science Implementation Network Group. She also represents trainees on the Royal College of Pathologist Specialist Advisory Committee for Genetics and Reproductive Science.

Lowri is an active STEM ambassador and is always enthusiastic and willing to promote the work of Clinical Scientists. Her energy and willingness to contribute is clear to all who meet her, but above all Lowri never forgets why she is doing what she does and that is for the benefit of patients."

The strong position of Genomics was further underlined with Angela Douglas being announced Healthcare Scientist of the Year and David Baty being NHS Scotland Healthcare Scientist of the Year. Congratulations to all!

So what are you waiting for? Get those nominations ready for the next round of award ceremonies!

Figure 1: Lowri Hughes with Prof Sue Hill Chief Scientific Officer and Prof Sir Bruce Keogh NHS England Medical Director.

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Editorial

Good morning everyone, and welcome to the new issue. Well, it is morning at the time of my writing this editorial; Monday morning no less, and a rainy one at that. But don't let your spirits be dampened, because we have a great issue for you to read, packed with lots of excellent articles.

This issue kicks off with a reflective piece written from the perspective of a trainee genetic counsellor who previously worked as a midwife, discussing the support offered to couples considering termination following chromosomal anomaly. I think it is interesting to see how our roles change when we swap between two related professions, as many of us have done who are now working as genetic counsellors. The AGNC Spring report contains information about new committee members, as well on-going projects relating to genetic counselling entry routes and sharing of good practice, which will be relevant both to us working in the field and new people entering it. The GCRB report outlines where we are up to with our AVR application, on which we should hear the outcome later this year; and also a reminder of the changes to renewal of registration and CPD.

As promised, we have reintroduced the profile piece, where we get to learn about each regional centre to get a flavour of what it is like to work there. This issue, the article is from the genetic counsellor team at St. George's Hospital, and I must say, it sounds like a great place to work. There are also reports from two conferences, IMPAHC and ESHG; so for anyone who missed attending these, you can catch up on some of the highlights in these articles. It sounds like there have been some very interesting and thought-provoking presentations and discussions at both.

Thank you to everyone who has contributed to this issue; I do appreciate the effort that everyone puts in to make this an interesting and relevant newsletter.

Happy reading!

Judith Edhouse

Supporting couples considering termination of pregnancy following diagnosis of a chromosomal anomaly; a trainee genetic counsellor's experience

Elspeth Graham (Aberdeen)

As a trainee genetic counsellor, I have been involved in the counselling of couples who have been found to have a pregnancy which carries a chromosomal anomaly, following chorion villus sampling (CVS) or amniocentesis. Couples are then promptly referred to the genetics clinic for discussion about options. Pre-test counselling is given by the obstetrician before any diagnostic procedure, and this includes discussion about the option of termination of pregnancy if a fetal abnormality, (TOPFA), is detected. The genetics appointment is offered within 24 hours of referral, and is always an emotionally charged appointment, allowing the couple to make a decision regarding their options.

Previously, I worked as a midwife in a ward caring for women with threatened or confirmed pregnancy loss. In the same ward, termination of pregnancy was conducted for fetal anomalies. I found this work emotionally demanding but sought to support each couple as professionally and empathically as possible at all times. I could see that it was never a straightforward process, with the couple struggling with every stage. My aim was to ensure that the couple were supported and never felt judged about the decision that they had made. Having already lost the hope of a healthy child, to then also make a choice about actively stopping the pregnancy must surely be the most difficult for anyone, even when the prognosis for the fetus is very poor.

I recall thinking that regardless of the difficulties encountered as a midwife I was relieved at not having to be involved in the decision making process. I sensed the difficulties would be even greater.

Now in my role within the Genetics team I have had some actual experience of those difficulties that I perceived. I appreciate that my role is primarily to give information regarding the condition that has been found in the fetus.

However it also involves helping the couple to consider what their understanding and beliefs are around the condition especially if it is compatible with life for example in Turners syndrome or Down's Syndrome.

Using counselling skills, we can help the couple to be open and honest with one another regarding their thoughts on the best decision for them to take as a family. We are also able to detect differences of opinion and facilitate how the couple may be able to resolve these. The time constraints to make a decision can sometimes impede clear thinking, together with the difficult decision they are considering.

I find this task a tremendous challenge despite having several years counselling skills experience in both my nursing career and in the voluntary sector. There is definitely something unique to this counselling scenario that creates an inner questioning of my own ability. There is so much to consider, including the language used to ensure no biases or personal views which may be perceived as guiding the couple. Perhaps my anxiety is borne from working with couples who have undergone a TOPFA and knowing that this entire experience stays with them always, especially so if secondary infertility becomes an issue.

Clinical supervision and peer discussion provides me with a space to share any concerns or doubts about this aspect of my work. As my knowledge and experience of explaining genetic conditions grows, I hope that I will have fewer doubts about my practice. With self awareness and the ability to examine and debrief after these appointments, I imagine my confidence will improve and ease my anxieties about whether I have done a good enough job at informing and supporting a couple at such a traumatic time in their lives.

One may never know fully how these families' lives are changed from going through an experience as described above. However, I hope that should they reflect on their time in the genetics clinic, they recall having gathered clear information in a non judgemental manner and with as much support as they needed.

AGNC Committee Spring Report 2015

Peter Marks, Birmingham

I write this article on the train from Glasgow, where I have spent the last four days at the European Society of Human Genetics (ESHG) 2015 conference. Not only have I been inspired by the wonderful host city but I also leave inspired by the talks, workshops and conversations with colleagues past and present. The dominant themes seemed to be around non-invasive prenatal testing and whole genome and exome sequencing. It was great to see so many genetic counsellors present at this important conference, many AGNC members. Attendance at these international meetings will be key to the development of our profession as the format of the annual BSGM meeting evolves.

Glasgow was also the venue for our AGM and I thought I would report back on the main discussions that took place. The minutes will soon be available on our website. Firstly, it was with pleasure that we were able to announce that Nicki Taverner from the All Wales Genetics Service was elected as the new member of our committee to start work in September this year. The committee looks forward to welcoming Nicki and working with her. In September, Liwsi-Kim Protheroe Davies will be stepping down from her role as Treasurer on the committee and Pam Harris will be taking on this role. We are really grateful for Liwsi-Kim's valuable work over the last six years. While Catherine Houghton is on maternity leave we felt it would be helpful to appoint a further committee member as soon as possible and so it was proposed at the AGM that we have a further election as soon as possible with the remaining candidates from the most recent election. They have all kindly agreed to stand again and there were no objections to this at the AGM. As such, you should all soon receive a further online voting request for this purpose. Also in September, Laura Boyes steps down from the role of Chair and Anita Bruce will be taking this on. Anna Middleton will be taking on the role of Vice Chair.

Catherine and I have been working on a project to promote the sharing of good practice between genetic counsellors working in different centres. The first part of this project has been the development of a survey to be sent to the lead genetic counsellor from each genetics centre. The survey gathers information about the pathway for managing predictive tests for conditions for which there is a therapeutic or risk-reducing intervention, including cancer predisposition syndromes and cardiac genetic conditions. The survey should be sent out later in June and we hope to publish the findings later this year.

AGNC Committee Spring Report 2015 *cont…*

Laura reported on progress towards the creation of a funded training pathway for genetic counsellors based upon the Modernising Scientific Careers pathway introduced for clinical scientists a few years ago. It is envisaged that this would take the form of a salaried, intercalated MSc and training post based in a Regional Genetics centre. The committee and a panel of members with experience in the field of education are in discussions with Health Education England (HEE) about this. If this pathway is agreed then the first cohort of students could begin in September 2016. There was agreement in the room that a funded training pathway would be a great opportunity for the profession but there were some understandable concerns about how long funding for the training will last and how the post-training registration landscape would relate to our current registration route. The committee shares these concerns and will, along with colleagues from the Joint Committee for Genetic Counsellor Registration (JCGCR), Genetic Counsellor Registration Board (GCRB) and Genetic Counsellor Training Panel (GCTP), be discussing these matters with HEE as the programme evolves.

It was exciting to hear that the GCRB, working alongside the JCGCR, have submitted their application for Accredited Voluntary Registration (AVR). The AGNC would like to thank our colleagues who have worked so hard on this important application and congratulate them on reaching this stage.

The committee have their next meeting on the 22nd June 2015. Items such as pending travel awards will be discussed at that time. Please continue to visit our website for further news updates and copies of minutes from previous meetings. The next two-day AGNC spring meeting will be hosted in Liverpool in 2016 and we will let you know the date of this once it has been finalised.

Feedback from the 14th International Meeting on the Psychosocial Aspects of Hereditary Cancer, (IMPAHC) 6 - 7 May 2015

Beverley Speight, Cambridge

This year's meeting was held at the Manchester Conference Centre. The staff and facilities at the Centre made it a good venue for the 158 attendees present over two days. There was time during breaks for poster viewing and the conference dinner took place at the Lowry Art Gallery in Salford Quays.

The first speaker, Professor Bettina Meiser (Sydney, Australia) described the outcome of her qualitative research on patient preferences regarding information derived from gene panel and whole genome testing. This topic led on to Professor Claire Foster (Southampton) speaking about web-based decision aids tailored to support younger women with breast cancer. Elizabeth Scully (Birmingham) gave an excellent summary of her MSc research, aiming to fill a knowledge gap on the psychosocial impact of living with Von Hippel-Lindau disease. This highlighted the value of health professional support, which may be lacking for family members, including unaffected partners.

Dr Nina Hallowell (Edinburgh) described results from her qualitative research on how individuals at high risk of hereditary diffuse gastric cancer decide between surveillance and surgery. It was helpful to learn about the factors which can contribute to the decision to pursue life-changing gastrectomy and how close relatives' experiences affect this process. Aptly chosen quotes helped the audience link the reported findings with the original data and conveyed the complexity of participants' decision-making.

Genetic testing for breast and ovarian cancer in Malaysia was the topic of two presentations, by Rifhan Azwani Mazlan (University Malaya Medical Centre) and Yoon Sook-Yee (Cancer Research Initiatives Foundation, Malaysia). We learnt that there are four genetic counsellors working in Malaysia and that uptake of genetic testing is low (even when cost and access are not an issue). In contrast, the qualitative data presented by Dr Hannah Shipman (Cambridge) derived from a rapid genetic testing project for ovarian cancer in East Anglia, provided evidence showing acceptability of genetic testing at the time of diagnosis.

Two speakers discussed their work on young women in hereditary breast and ovarian cancer families. Dr Allison Werner-Lin (Philadelphia, USA) controversially described autonomous decision making regarding *BRCA1/2* predictive testing in 18-24 year olds as a "pipe dream", leading to questions from the audience.

IMPAHC feedback *cont…*

Dr Laura Forrest (Melbourne, Australia) presented her research on *BRCA1/2* carrier women's decisions about breast screening and surgery. She made some interesting comments about the difficulties women who delay surgery in order to breastfeed may face when needing surgical recovery time whilst parenting young children.

The second day began with a session on hereditary childhood cancer. Dr Andrea Patenaude (Boston, USA) focussed on the ethical and psychosocial issues, including the additional parental burdens of self-blame and risk to other children at a time of high stress and diminished resources.

Dr Claire Wakefield (Sydney, Australia) presented her work on the needs of childhood-cancer survivors, with her main findings being that written information on cancer genetics was an unmet need, and that many had personal theories for the reason for their cancer that they did not share with their doctors. Dr Kathryn Kash (USA) then gave an overview of the psychosocial implications of new directions for genetic testing, particularly identifying the growth of direct to consumer testing and non-invasive prenatal diagnosis. A theme arising from this session was the increase in children being found to have mutations in adult-onset cancer genes, as more undergo genomic or panel testing.

Later on, Dr Laura Forrest (Melbourne, Australia) presented useful findings on the return of clinically significant mutations by research studies. When participants were notified only by letter, fewer than half responded. This was improved with addition of a telephone counselling session two weeks after the initial letter, which can be offered centrally and inexpensively.

Lastly, Professor Gareth Evans presented data from the PROCAS study which is stratifying both familial and population breast cancer risks using Single Nucleotide Polymorphisms (SNPs) and breast density. We heard that SNPs are ready for use in giving women with *BRCA2* mutations a more personalised estimate of their cancer risk to aid their decisions about risk management. Another interesting aspect of this study is its ability to identify women who are at low risk and may not benefit from population screening, although it was recognised that overcoming the widely held belief that screening is beneficial may prove challenging.

This IMPAHC meeting was well organised and provided plenty of relevant and stimulating material for anyone interested in the psychosocial impact of hereditary cancer. The next IMPAHC meeting is planned for May 2017 and will be held in Kuala Lumpur, Malaysia.

Genetics Heroes

Anna Lehmann and Glen Brice, St. George's

St George's is one of the largest teaching hospitals in London. Founded in 1733, the hospital was originally based in central London on a site which now houses an upmarket hotel, The Lanesborough.

Our medical school was established in 1868 and the hospital moved to the curry capital of London, Tooting, in 1973. Following the opening of London's second Helipad trauma centre in May 2014 on the roof of the hospital, St George's was chosen as the site of filming for the seventh series of *24 Hours in A&E*.

Far beneath the ground and the glamour of the helipad heroes, featured in *24 hours in A&E*, and possibly a little more sedate, lies the genetics department, founded in 1986. The department is filled with a team of genetics heroes who carry out a wide range of clinics both locally and in peripheral hospitals all the way down to the south coast.

We are currently a tight knit team of eight genetic counsellors who run regular cancer and general clinics in more than 18 different hospitals around South West London, Surrey and Sussex. We have a genetic counsellor-led triage system for cancer referrals which has been developed alongside our in-house database, to allow for a more automated process of information gathering and administration of appointments, relating to family history assessment. We have also forged specialist links for genetic counselling in multidisciplinary environments including the fetal medicine unit, dermatology team,.

Genetics Heroes *cont…*

and the cardiology departments at St George's, The Royal Brompton and Harefield Hospitals

Working alongside the genetic counselling team are eight consultant clinical geneticists also with diverse specialisms, whose depth of knowledge and compassionate care for their patients is second to none.

Our genetic counselling team is led by Glen Brice, who began working at St George's on Valentine's Day 1988, beginning a love affair with the hospital that has lasted for 27 years. He began in the genetics department in 2002. Other team members are Ginny Attard, Charlotte Eddy, Lizzie Winchester, Sarah Bennett, Jessica Bailey, Gaya Connolly and Anna Lehmann.

Our department has changed in many ways over the years; the number of clinical staff has increased including the number of genetic counsellors which has grown from three to eight, in order to deal with the increase in referrals and growth of our service. We see many more patients and, with our increased workload and interaction with other teams, our profile within the hospital has greatly increased. Over the recent years our cytogenetics and molecular laboratories have also merged to become one unified laboratory.

The genetic counselling role has also broadened over the years so that genetic counsellors at St George's now have more autonomy and a greater input into the departmental management, with a genetic counsellor forming part of the executive team and leading on clinical governance. We also welcome a steady stream of genetic counselling students including the occasional guest from overseas.

In order to facilitate continued professional development and safe practice we receive regular supervision, and have worked to pioneer a model of accredited supervision. This model involves both a restorative and a psycho-educative aspect to supervision and modules are assessed at the end of our chosen topic.

The genetic counsellors at St. George's (left to right): Glen Brice, Virginia Attard, Jessica Bailey, Sarah Bennett, Charlotte Eddy, Anna Lehmann, Elizabeth Winchester, Gaya Connolly

Members of the genetic counsellor team have suggested their favourite things about working at St George's are the friendliness of our team, the opportunity to work with experts in a wide variety of specialisms, the ability to get involved in teaching within the medical school, being involved with national research studies, the diversity of population we serve, and not least the proximity of Peabody's coffee shop.

Genetic Counsellor Registration Board (GCRB) update

Diana Scotcher, Chair, Manchester
and Diane Stirling, Deputy Chair, Edinburgh

Accredited Voluntary Registration (AVR) with the Professional Standards Authority (PSA)

The Professional Standards Authority (PSA) accredits regulation of statutory and voluntary professional organisations. The GCRB and the Joint Committee on Genetic Counsellor Registration (JCGCR) have been working towards voluntary regulation for genetic counsellors.

We would like to update you on the progress so far and plans for AVR.

- December 2014: The GCRB submitted an application for AVR with the PSA.
- March 2015: The GCRB application was reviewed by the PSA and we were given detailed feedback including suggestions on how to enhance the application.
- June 2015: with support from the AVR team, the GCRB submitted an amended application.
- Summer 2015: The AVR team carefully review all documentation and systems within the GCRB, interview the GCRB members, and observe GCRB meetings. They make suggestions about how we should alter any aspects of our work.
- 2015: Once the AVR team are satisfied that the GCRB reach the standards expected by the PSA, the application and AVR reports will be reviewed by a PSA Panel.
- Late 2015: we will hear if the application has been successful.

We will keep you informed of progress.

GCRB Annual General Meeting (AGM)

The AGM was held on 8th June 2015 at ESHG conference in Glasgow. The meeting was well attended by over 50 genetic counsellors. While the membership was given a brief overview of GCRB activities during the year, a highlight was a first viewing of the prototype for the new GCRB website presented by Cathy Watt. The application for AVR will be strengthened by the new website, which will include information for patients, the public and employers, about the training, role, skills and expected competencies of a genetic counsellor, and include a section on how to raise a concern or air a grievance. The first phase of the website will be launched in the near future. The second phase will include an online facility for payment of fees for GCRB Registration and annual subscriptions, and a membership section for members to check their details and registration and mentorship status.

Accreditation of UK MSc Genetic Counselling programmes

The GCRB accredits MSc Genetic Counselling Programmes every three years, to ensure that they offer teaching and learning that gives graduates the competences for GCRB registration. The GCRB were delighted that the programmes at the University of Manchester and Cardiff University were successful in their applications for re-accreditation in 2014.
An interesting addition is that the team who teach the MSc in Medical Genetics at the University of Glasgow are developing an MSc in Genetic Counselling in collaboration with the West of Scotland Genetics Service.

The application for accreditation of this new programme is being reviewed by the GCRB.

Renewal of GCRB Registration

The GCRB recently reviewed the renewal of registration process, which continues to be every five years. This is independent of payment of annual subscription fees. There are no major changes to the documentation regarding renewing registration. However, in future those not submitting their five-yearly GCRB renewal of registration documentation (including CPD) by the May 1st deadline will be fined £100 and will be expected to submit their complete documentation by June 1st of the same year. After that date GCRB registration will be considered lapsed. If for any reason a genetic counsellor has reason to delay renewal of registration they can submit an extenuating circumstances form, with supporting evidence. This is available from the GCRB Administrator or the new website.

Continuing Professional Development (CPD)

The guidelines for CPD have been amended to make it clear what aspects of learning can and cannot be included in CPD. The CPD guidelines now stand as a discrete document and apply to genetic counsellors who are registering for the first time or renewing registration. These guidelines will be on the new GCRB website.

Sign-Off Mentor (SOM) Training

SOMs play a crucial role in the GCRB registration process and work with applicants to support and guide them during the preparation of their portfolio prior to submission. Training courses for SOMs are held annually and the last one was 10th June 2015 in Glasgow, attended by 19 Registered Genetic Counsellors with at least five years' experience. SOMs should attend a training course every three years in order to continue in the role.

Please contact the GCRB through the Administrator Chris Barnes on cabarnes@blueyonder.co.uk if you have any queries relating to registration or the work of the GCRB.

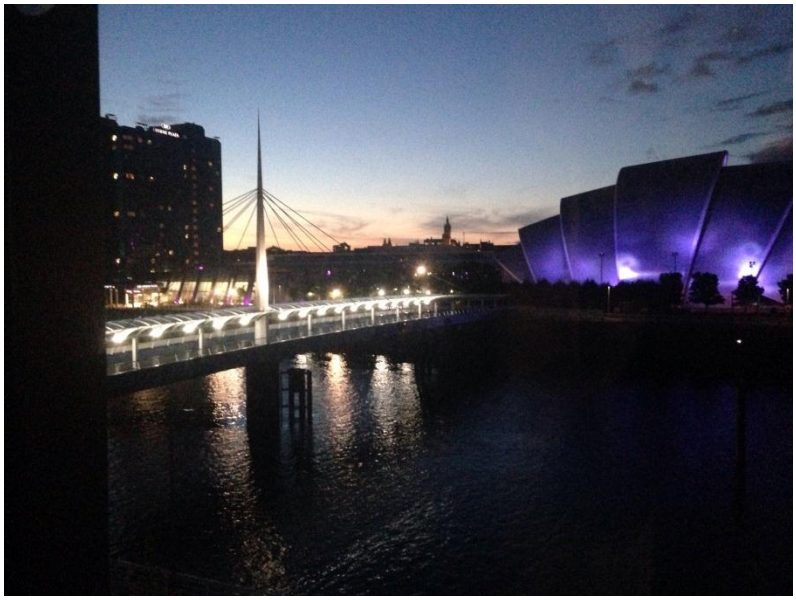
Report from the European Society of Human Genetics (ESHG) conference, Glasgow, June 2015

Tammy Kammin, Boston, USA
and Shan Owens, Hywell Dda UBH/All Wales

Feedback from Tammy

For the last 18 months, I have been working as a research genetic counsellor on the Developmental Genome Anatomy Project (DGAP) study, based in Boston, USA. This study uses next generation sequencing to investigate the developmental abnormalities in patients with apparently balanced chromosome rearrangements. As much as I enjoy being part of the American research world, I was excited to attend my first ESHG meeting; particularly to learn about new research and clinical developments in the European genetics field, and hear the thoughts of the European genetics community. Being originally from the UK, I was also looking forward to returning home and catching up with my British colleagues with whom I remain in close contact.

The meeting did not disappoint. In true Scottish style, the weather on the first day was cold, rainy and windy; however, this did not dampen the excitement inside the conference. The highlights on the first day were the CRISPR-Cas9 discussion and the Non-Invasive Prenatal Test (NIPT) presentations. Both sessions stimulated great discussion at the evening networking mixer which was held in the Glasgow Science Centre, a unique and fun destination. The Scottish hospitality continued with bagpipers and hors d'oeuvre which included mini Angus cheeseburgers and curry-themed snacks. It was here where I met several colleagues from Europe, who have sent samples to me for our DGAP study, and it was great to finally meet them.



The conference centre in Glasgow, known affectionately as the armadillo

The meeting (and the weather) continued to get better and better over the following days with sessions on reproductive genetics and cancer genomics being some of my favourites. The workshop on palliative care led by geneticists in the Netherlands, where euthanasia is legal, was also poignant and eye opening. On the Monday, I presented a poster on my research work, where I was rushed off my feet discussing all aspects of chromosome rearrangements. I also met the lovely Shan from the Welsh genetic counselling team.

In summary, the meeting was a wonderful mix of the latest research intertwined with stirring ethical discussions, and I have returned to Boston with fresh ideas and different perspectives. There was a large group of UK and Irish genetic counsellors at this meeting, many of whom gave excellent presentations and I really enjoyed saying hello.

Thank you very much to the AGNC for the opportunity to attend this prestigious meeting.

Feedback from Shan

It was an eye opener to attend such a multinational conference. Although a European event, participants attended from around the globe, though I didn't hear any Welsh. I wasn't really sure what to expect but was overwhelmed by the amount of spoken and poster presentations. There were too many posters to view in the time available and pre-planning was required, so I resorted to taking photos of posters to read at a later date. From a personal perspective it would have been nice to see some of the sessions repeated to allow access to different subject areas. Although a very tiring, this conference has reinforced the importance of having access to national conferences to hear about and discuss new findings. It will take a while to absorb the content of the four days.

The venue was fantastic, with plenty of space. Sitting in the main auditorium to listen to the opening address I was staggered by the numbers attending. It took me back to my early days in genetics when the BSHG conference attracted a' full house'. The IT revolution was apparent, with many using laptops and other gadgets to take notes, download abstracts and check web sites. I could not believe the phone charging station! This was a theme for discussion in terms of global data sharing; how this can be achieved within a governance framework and be securely stored.

Considering we generally consider communication to be an important aspect of our role I was struck by how nationalities interpret words in different ways. This is particularly relevant to the updated position statements from the American Society of Human Genetics on genetic testing of children and adolescents, and is a possible reason for discrepancy in interpretation. It was healthy to address this, and I suspect it will raise a few more questions once published.

Whole genome wide testing was discussed and debated in many sessions, not least the great debate, which asked the question "should all geneticists have their genome sequenced?" Some members of the audience shared personal experiences cautioning on some of the wider implications of testing. If we give our families choice, then I would expect the same for professionals.

Shan Owens (L) and Tammy Kammin (R) in front of Tammy's poster

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Editorial

Derek Lim

Summer and good weather is finally here. No doubt most of us have been busy with our clinical workload. I would like to take the opportunity to welcome Ruth Newbury-Ecob as our new president of the CGS and to thank the outgoing president (now vice-president) Jill Clayton-Smith for her contributions not only to the CGS newsletter but of course the tremendous amount of work with the CGS.

The flavour of the season continues to be the 100,000 Genomes Project. Personally, being involved in advising the local informatics team and helping to start up recruiting clinics in my local Genomic Medicine Centre (GMC) have been an eye-opener in terms of the scale of the project and the specific requirements of Genomics England (GEL). Working together with colleagues in non-genetics specialties in this aspect have been challenging but also very rewarding in seeing the steep learning curve in their understanding of the genetics of rare diseases and the importance of good phenotyping data and family information. Crucially, as outlined by our president Ruth in her President's Report, the experience has given a little taster into how we, as clinical geneticists/genomicists will have to play an important role in a multi-disciplinary team (MDT) setting.

While we are still in the midst of the fever of the 100,000 Genomes Project, the title of the CGS Medical Student Essay Prize for 2015 have been chosen to examine the views of budding doctors on the project. The title selected was "The 100,000 Genome Project promises to improve the health and wealth of the nation: Can it deliver?". I am pleased to announce that Marianne Shawe-Taylor from the University of Liverpool was chosen as the winner among tough competition and she wins a prize of £300 and a certificate from the CGS. Her excellent essay which examines the various aims of the project is presented in this newsletter and I urge you to read it.

In a previous newsletter, Charles Shaw-Smith presented the formation of the Clinical Genetics IT leads group which meets annually to discuss the IT requirements and issues in clinical genetics and the move towards electronic clinical genetics records. One of the aims of the groups is to learn what each centre is doing with regards to moving to electronic records, the challenges they face and lessons learnt. At the most recent meeting which took place at the ESHG conference, we heard the experiences from Cambridge and Aberdeen in moving towards their chosen systems and they have kindly agreed to share in a future newsletter. There are pros and cons with each system and it was very helpful to hear about the advantages and limitations of the various systems used. Some departments take the lead in deciding on their own system whereas others are led by global adaptation of a system by their whole hospital or regional Trust. Another point highlighted is that specific requirements of each regional clinical genetics department (e.g. the requirement to work offline at peripheral clinics) will make a universal one-size-fits-all system impossible. Previously, Pradeep Vasudevan from Leicester presented the experience of going electronic in Leicester and in this edition of the newsletter, Kai Ren Ong from Birmingham presents the West Midlands experience using an electronic document management system that allows offline working using a laptop which is synchronised on return to the department.

Also included in this edition, is a proposed interim management guidelines on the management of hereditary haemorrhagic telangiectasia (HHT) by the North of UK Vascular Genetics Guidelines Group (NOUV-GGG).

Conference season is also amongst us and following on from a very successful CGS Spring meeting in London, the European Society of Human Genetics (ESHG) conference was held in Glasgow this year in June. The attendance at this meeting among the UK genetics contingent this year is significantly higher with many taking the opportunity to attend with it being in the UK and in conjunction with the BSGM with no separate BSGM conference this year. The use of Twitter to tweet highlights of the conference using hashtags #ESHG15 and #ESHG2015 was a hit and a useful way for those unable to attend to receive highlights. You can read highlights of the ESHG conference from Hannah Titheradge who recieved a bursary by the CGS to attend and present her poster at the conference.

Finally we bid farewell to Hannah who steps down at the end of her tenure on CGS council as SpR representative and welcome Rhoda Akilapa as her replacement.

President's report

Professor Ruth Newbury-Ecob, Bristol

Firstly, can I say a huge thank you to Professor Jill Clayton-Smith, outgoing President, now Vice President, for her hard work over the last two years. She has steered the society on a steady course at a difficult time.

Clinical geneticists are facing huge challenges juggling multiple demands for their unique expertise. At the recent Lead clinicians meeting we saw evidence and learnt of the unprecedented increase in numbers of referrals into clinical genetic services across the UK. It is no wonder that we are all feeling over stretched. In light of this, Jill, myself and Lynn Greenhalgh arranged a two day working party in Birmingham with the Lead Clinicians' Group , CGS Council and invitees from mainstream specialties, primary care, laboratory services and genetic counselling to discuss the changes to our role likely to take place over the next few years. A summary document *The evolving role of the clinical geneticist* is being finalised and will be circulated soon. It recognises the pressures that most of us are feeling in relation to the increased availability of complex genetic testing requiring clinical evaluation and interpretation. This area of our work has largely been unrecognised in the past and it is anticipated that we will need to make time available for our own cases and play a significant role in multidisciplinary teams (MDTs) for mainstream specialties. Within the document is interesting and helpful feedback from cardiologists, oncologists and primary care physicians about how we may best work alongside colleagues and what they think of our services. An ability to talk their language and communicate effectively about genetics were high on the list of desirable characteristics for clinical geneticists.

Above all, it is clear that the role of the clinical geneticist for the next decade will require increased knowledge of genomics and bioinformatics. There are two initiatives currently seeking to provide us with the necessary education. The PG certificate devised by Dr Kate Tatton-Brown at St George's Hospital is aimed particularly at specialist registrars. The Health Education England (HEE) MSc programmes in a number of centres provide an alternative. Discussions took place recently at Council about ensuring availability for trainees and consultants around the UK.

For the meetings that I have attended so far in my capacity as President, the 100,000 Genomes Project dominates the agenda alongside a number of initiatives around rare disease commissioning and service development. Professor Jill Clayton-Smith has kindly summarised the multitude of committees involved and the links to our European partners, the European network of specialised services and the rare disease translational research collaboration. The debate at the European Society of Human Genetics (ESHG) asked if we should lead in having our own genomes sequenced. *23&me* now have analysed over 1 million cases. Dr. Anna Middleton's study of what people "do" with their genome found that 51% would find a geneticist to help them interpret it suggesting that we will have a crucial role as the uptake increases and as next generation sequencing (NGS) technology is introduced into mainstream medicine. Clinical geneticists have an important contribution to make to ensure that this is freely available but undertaken in an appropriate and useful way.

The Glasgow Deciphering Developmental Disorders (DDD) collaborators meeting showed what a phenomenal success this collaborative project involving all the 23 regional genetics centres has been, with answers being provided for families alongside the identification of new syndromes and genes. It places rare disease research firmly in the spotlight and is the envy of the world. I chaired a joint session between the ESHG and the European Society of Cardiology on rare variants in common disease from which the take home message was that rare variants are useful for stratified medicine and that loss of function mutations identified through Mendelian cases are often the best route into therapies.

There have been a number of changes in the CGS Council. We welcome the expertise of Dr Diana Baralle as Treasurer and Dr Lynn Greenhalgh as Secretary. We are very grateful to Professor Peter Farndon who has stepped into the gap occurring in the absence of Mrs. Dina Kotecha who is currently on maternity leave. Following the recent difficulties the CGS is working with BSGM to look in depth detail at our governance arrangements and structures, roles and responsibilities and liabilities of the officers. We are hoping our website will be re-vamped thanks to Rhoda our SpR rep on Council working together with BSGM. If you have articles you think will be of interest or adverts, please send them to us and we can arrange for them to be uploaded to the site which we hope can become a more useful tool.

Professor Dhavendra Kumar organised the CGS meeting in London in March which was a huge success. The standard of presentations amongst the trainees was particularly high and a difficult decision had to be made regarding the winner of the Robin Winter Prize which was awarded to Dr Madeleine Tooley from Bristol. We look forward to a two day meeting in Cardiff jointly with the Cancer Genetics Group and Dutch Clinical & Cancer Genetics Groups with an excellent programme, to include sessions on neurogenetics, craniofacial disorders and angiogenesis. I hope very much that you will be able to join us as we know the survival of the society will depend on attendance at conferences.

Finally, I hope you all had a warm and sunny summer and opportunity to rest and recuperate following what I suspect has been a particularly busy and demanding year.

CGS Essay Prize: The 100,000 Genome Project promises to improve the health and wealth of the nation: Can it deliver?

Marianne Shawe-Taylor,
Year 4 Medical Student, University of Liverpool

In December 2012, the Prime Minister announced the '100,000 Genome Project', proposing the sequencing of 100,000 genomes of sufferers of known cancer, rare inherited diseases and infectious diseases. The project will collect a wide range of genomic information, which can be applied to medicine and public health, and allow an increased understanding of disease aetiology, diagnosis, treatment and prevention. [1] Whether or not this is likely to improve the health and wealth of the nation is an interesting question. The project has certainly embarked with high aspirations, sequencing a large number of genomes, in order to attempt to cover a large breadth of the population. It has also presented itself as the pioneer for 'personalisation of medicine', wherein all persons shall have their perfect cure. However, investing so much hope and financial weight into one 'all-curing' idea, seems to be a way of seeming to be tackling many problems at once, but not moving forward with any of them.

The project could be used to generate a database of genomic information, around a myriad of diseases, which would ensure that all those at risk were given adequate screening to prevent symptoms. This has already been seen within the UK, with the annual testing (MRI or mammography) for patients found to have the BRCA1/2 gene.[2] This has allowed patients with a known risk to alter their lifestyle choices as much as possible to reduce their risk, and even request medical interventions, such as prophylactic mastectomies, to reduce their risk of breast cancer by 90%.[3]

However, knowing every medical condition to which you had a predisposition could lead to unnecessary fear and lifestyle changes. Sequencing patients would show mutations which may never have manifested into a disease. This could cause an increased demand for expensive and dangerous 'prophylactic' operations, or multiple testing for every minor symptom. There would also be the psychological burden of this information, with a complete change in what it means to be 'healthy'.[4] Research identified a high (20%) risk of post-test result depression and anxiety for those with BRCA1/2 genes.[5] This demonstrates that this information could inflict harm as well as highlighting at risk patients. Preserving the health and wealth of the nation in the face of tangible adversity is already difficult enough.

The health of the populous may have the potential to be increased by genomic knowledge via interference with Natural Selection. Couples with known risks for diseases within their DNA may decide not to have children, or decide to use IVF to allow themselves the option of which genome they would implant. However, this would come at the cost of all the potential beneficial changes within the de-selected genomes. There would also be massive ethical and legal issues – all of which would be costly to tackle, and unhelpful to the health of the nation.

Advancement in treatment is what we are hoping to expect. Already, 60% of preclinical developments of treatments rely upon biomarker data, and 10% of drugs already marketed will recommend genetic testing to ensure optimal treatment. Thus, a move towards personalised medicine, based on the ideology of a treatment entirely specific for the pathophysiological process, with as few as possible side effects for the patient. Therefore, in order for such treatments to be developed, the understanding and identification of the genes associated with each target disease must be identified.

Within oncology, genetic information would also be helpful in the understanding of the tumour biology. As yet the complicated nature of cancer has meant that the personalisation of treatments is impossible, and thus its treatment has the reputation for being a barrage.[6] With a greater understanding of the DNA within individual cells could come knowledge of: the biomarkers and therapeutic targets, the downstream signaling pathways from the tumour, and the tumour's effects upon different DNA/RNA related enzymes.[7] With this, selection of an ideal chemotherapy regimen could be made prior to its commencement (rather than by a trial-and-error process). This will not only allow for the optimum cytotoxicity for the disease, but also limit the number of unpleasant side effects. Here there is the hope of improving the prognosis of cancer, and the timeline of disease, and thereby changing the way that a diagnosis is viewed.

Genomic sequencing would not only affect cancer patients. The field of enquiry is also turned towards those with infectious diseases, another area of medicine much in need of new innovation. Whilst incidences are declining in the UK, thanks to better understanding of cleanliness and hygiene, the financial burden still remains high, at approximately £30 billion per year. We are also faced with the major risk of increasing antibiotic resistance, currently 800 laboratory reports of Enterobacteriae which can cause antibiotic resistant sepsis (associated with a 30% mortality).[8,9]

Therefore, identifying a genetic basis of vulnerability could provide the option of prophylactic gene therapy (once this art has advanced). This would not only prevent patient morbidity, but also decrease the necessity of antibiotic prescription, and decrease the likelihood of new resistance development.[10]

From a financial point of view, it is difficult to postulate the effect of the personalisation of treatment. At present current spending on cancer alone is approximately £30,000 per patient, and so a more frugal mode of treatment is a necessity.[10] With the switch from a battery of chemotherapeutic regimens, to one cleverly selected option, you are already potentially saving large sums. One study, investigating the cost-effectiveness of chemotherapy in breast cancer found the various side effects alone cost $1271 per person per year.[11] However, to make a real fiscal difference, the personalised hitherto discussed would be ideal, and whilst this would be marvelous - as yet these drugs are not available, and in order for them to become so, large sums must be invested into their development and testing. Even then, the patent upon new treatments would last a long time, thereby making the likely cost astronomical. The financial effect of these treatment changes is therefore hard to fathom.

In theory personalised medicine has a whole host of benefits, but they are simply not yet available. Unfortunately, there is also no immediate hope for them. The delay associated with the project, added to the time associated with making any drugs available (which averages approximately 10-15 years) will leave a large period of time before the nation can derive the benefits.[17] Even then, drug companies in a hurry to meet the demand, for what will be very sought after treatment, may rush their usual testing protocol, and potentially harm the populous.

The cost of the project - £100million government funding - also diverts resources from other strands of research, which could better the health of the nation. Even with completed data from this project, we are still many steps removed from any health or wealth benefit we may see. When patterns of underlying genes have been identified, vast amounts of work will need to be done on the process by which this aberrance transforms into the pathology. A review of the advancement of personalised medicine in Hungary proposed a triad of: pharmacogenomics, biotechnology and regulatory issues as a necessary background for genomic medicine's success.[12] However, in Hungary, as in the UK, the distribution of funding does not reflect this. Relying on the DNA code as an answer for every nuance of disease is too simplistic. Hence, after 10 years of investment in the Human Genome Project by the US Food and Drug Administration, only a very small number of drugs based upon genetic biomarkers alone are available.[13]

Classification of disease is an area where this project has potential use. Classifying more exactly in this way would also allow more accurate separation of 'diseases'. Currently, diseases are commonly based upon a recognized collection of symptoms, and findings upon examination. However, with knowledge of the genomic component could come more better distinguishing features.[14] This could be very beneficial for pattern recognition. With increasingly specified data, it would be easy to note the interplay that environmental risk factors may have with different genotypes. This would allow a clearer estimate of a person's risk, based not only upon their genes, but also their lifestyle choices, age and gender.

Cleaner differentiation would also allow a clearer understanding of the likely course of disease for that particular patient. For some, these patterns could allow a more accurate prediction of prognosis. This would be much to be desired as, at present, a systematic review (covering over 1500 predictions of survival in patients with cancer) saw that the predictions were accurate within a week for less than 25% of cases.[15] From the point of view of patients, an improved accuracy could have financial implications (the need to set ones affairs in order), as well as giving families realistic expectations. The timely switch from curative to palliative care would also save the patient from crippling and unnecessary side effects, and save on the NHS budget.

Assessing the project's value against utilitarian principles is essential. Whilst there are a great deal of potential benefits, they would only affect a small number of patients.[16] At present the prevalence of these conditions is understood to be very low. The BRAC1/2 gene mutation, for example, is estimated at between 0.07 and 0.09% of the population. In comparison, the prevalence of obesity (another risk factor for breast cancer) is 62.1%.[17] This demonstrates funding being thrown at a rare, but potentially more interesting, problem, rather than meeting the need of the population as a whole. There could also be the dangers with dividing up patients with cancer into those with a genetic predisposition, and those who, by their poor lifestyle choices, 'deserved' their diagnosis. It would inflict guilt on the latter, and, perhaps unfairly, absolve completely the former. Allocating resources preferentially based on genome would be an over simplification of the interaction between lifestyle and genetic factors.

The choice of conditions also seems too broad. Rather than deciding to sequence more patients of the same disease, in order to gather a strong bank of genetic information which could be considered statistically robust; the project has decided to sequence over 7,500 rare diseases.[18] This ensures a fair approach, maximising benefit to the most people. However, it may compromise the usefulness of the data, and, since the conditions are almost being selected for their rarity, returns to the issue of distributive justice in a population of limited resources.

In conclusion, therefore, the enthusiastic sequencing of such a large cohort of patients will allow a good basic understanding of the genomics underlying the processes. This could have some benefit, given time, in the treatments administered to them, and hopefully decrease the burden on patients, their families, and also the NHS and its limited budget. The knowledge could also lead to a database of at risk patients, for whom monitoring and added advice would be essential. However, the promise to improve the health and wealth of the nation is too grandiose. The health of the nation is unlikely to be improved until there are treatments available to target these newly identified mutations. The wealth, on the other hand, is markedly reduced by the financial drain of the project, which will not decrease the necessity for expenditure in the near future, such as to even hope to make a return.

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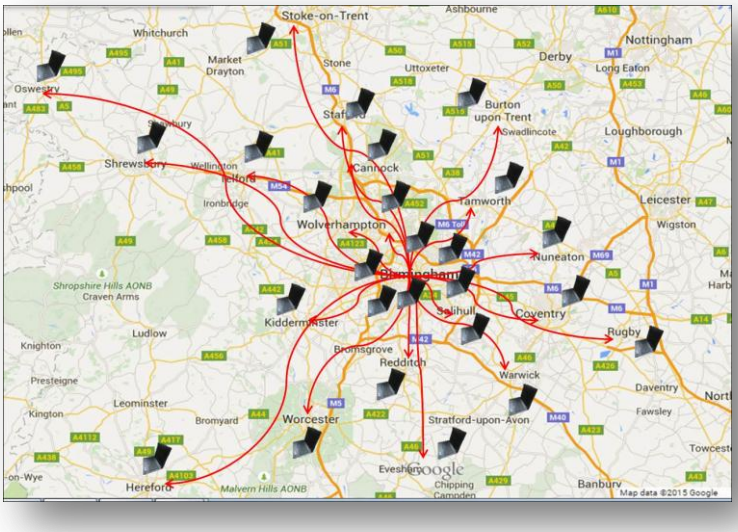
Going electronic – the Birmingham experience

**Dr Kai Ren Ong, Clinical Lead,
West Midlands Regional Clinical Genetics Service**

The push to digitise patient records is one of the NHS' major projects and a target of 2018 for a "paperless NHS" was set by the government in 2013. Since 2013, the West Midlands Regional Genetics Service based at Birmingham Women's Hospital has been using electronic patient records within the cancer genetics service. Before the implementation of the electronic system, we had approximately 21000 paper based cancer genetics records. Paper files contain all the individuals within the family, with each member having a separate "point number".

Documentum was chosen after a lengthy tender process. Responders to the tender were shortlisted and invited to present their system to the clinicians; the ability to take information offline to clinic and integrate process workflows with our database were important factors in choosing the best system. Documentum was a clear winner. Separately, several methods for scanning were evaluated, balancing the scanning effort against the usability of the resulting electronic file.

Starting in 2011, the interface was designed and developed. Documentum, the electronic document management system, displays the patient documents and allows management of the staff workflow. It works alongside the Clinical Genetics Database (CGDB). The CGDB contains patient details, and the integrated care pathway in which clinical decisions are recorded, letters generated, and tasks for clinical and administrative staff assigned. Letters produced through the CGDB are automatically filed in the electronic record in PDF format. The Pedigree Assistant software is also integrated with Documentum and any updates to a pedigree are easily filed into the record.



Ability to work offline and synchronise at base an important requirement due to widespread geographical locations of clinics across different trusts

The system was implemented in spring 2013. Clinical staff manage their day to day work through the system, with a "workqueue" containing tasks, ranging from new referrals to review, triage following return of a family history form and clinical information, pre-clinic preparation, review of new results and correspondence, and requests between clinicians to respond to questions about a case. Administrative staff scan incoming documents within a few days and direct these via the workqueues to the relevant clinician. The administrative staff also have their own workqueue, containing newly generated letters for printing, family history forms from which to enter data, additional information requests e.g. DNA banking and tissue block testing and other queries from clinicians.

The online records can be downloaded to a laptop and viewed in an offline viewer when off site at peripheral clinics. All clinical staff have now received new laptops from February 2015. Clinical notes can be typed offline and synchronised to the online record on return to the department. Electronic pedigrees can be exported to the laptop via Pedigree Assistant, edited in clinic and updated on return to the department.

Clinicians, our own IT developers and the administrative staff constantly review the interface and we have gradually resolved various imperfections and improved usability. It would be true to say that working with electronic records "takes some getting used to". The ability to visually scan through a thick set of notes is lost and this can be frustrating in the heat of a busy clinic, but the organisation of large sets of notes is generally better and notes no longer go missing. It is hoped that newer packages for offline viewing may improve the ability to view documents quickly when in the clinic.

Going electronic – the Birmingham experience cont…

One of the great advantages to the electronic system is the ability for multiple individuals to view a family record and take this to clinic simultaneously.

Approximately 8400 new referrals have been immediately digitised and never created as a paper file since 2013. Paper records that become active (i.e. re-referrals returning to clinic, new family members added to a family file) are scanned. The paper records are currently being stored but following a satisfactory audit of quality control processes, we will destroy scanned paper records. A decision has yet to be made whether we will carry out whole scale scanning of all records at some point in the future.

We are now developing the system for non-cancer genetics with the creation of an electronic Integrated Care Pathway (ICP) and modifications to the system to accommodate the needs of general genetics cases, e.g. inclusion of photographs.

Change is never easy and we do not anticipate that the full roll out will be without some difficulties despite considerable experience from the cancer genetics service. However, we all appreciate the advantages of electronic records and are willing to embrace the transition, and clinicians and administrative staff are enthusiastic to participate in making a user friendly system which fully serves ours and the patients' needs.

Management of Hereditary Haemorrhagic Telangiectasia (HHT) - an interim guideline

North of UK Vascular Genetics Guidelines Group (NOUV-GGG):

Professor Mary Porteous, Consultant Clinical Geneticist, Edinburgh
Dr Jenny Thomson, Consultant Clinical Geneticist, Leeds
Dr Graham Robinson, Consultant Vascular Radiologist, Hull
Dr Jonathan Berg, Hon. Consultant Clinical Geneticist, Dundee

Existing guidelines for the management of HHT continue to be problematic, with little evidence underpinning current practice.[1] In order to be able to move forward and provide care for patients, there is a need for pragmatic guidance based on expert opinion.

Management in pregnancy

Nosebleeds and Telangiectases
Some papers suggest that symptoms can deteriorate in pregnancy.[2] A pragmatic approach would be to monitor for anaemia and refer to ENT surgeons for treatment if required.

Anaesthetic techniques in labour
There are single case reports of spinal arteriovenous malformations (AVMs) in the literature, and discussion of the most appropriate management of women with Brain AVMs (BAVMs) in pregnancy. However, there is no evidence that Spinal AVMs or epidural AVMs present a significant risk in women with HHT who are pregnant. The most informative case series by de Gussem et al. reviewed 92 epidurals with no complications in pregnancy.[2] There is currently, therefore, no evidence to support spinal MRI or CT in women likely to need an epidural or spinal anaesthetic.

Management in neonates and children

Appropriate assessment after delivery
There is no evidence to support any additional specific assessment of neonates where a parent is affected with HHT.

Screening for Brain AVMs (BAVMs)
While there are a number of case reports of severe perinatal complications caused by BAVMs and brain arteriovenous fistulas (BAVFs), there is no evidence of benefit in routinely screening neonates or children for BAVMs/BAVFs. However, there are no clinical trials to date that have satisfactorily investigated this issue.

Screening for Pulmonary AVMs (PAVMs)
Presentation of symptomatic PAVMs in children is rare. There is no evidence to support screening of children for PAVMs in the absence of symptoms of hypoxia. In the presence of symptoms of hypoxia, then assessment should be in line with local protocols, and may include pulse oximetry, contrast echocardiography and/or CT Pulmonary Angiography (CTPA).

Gene testing in children
There is no indication for routinely gene testing asymptomatic children at risk of HHT, although gene testing may be appropriate, for example to avoid unnecessary investigations involving ionizing radiation in children found not to have inherited an HHT gene mutation.

Management in adults

Screening for PAVMs
Identification and treatment of PAVMs in adults is recognized to reduce risk of complications. Lesions do increase in size at puberty and in response to hormonal influences. Screening for PAVMs should take place after puberty as a baseline. Further data is required to establish whether subsequent screens are required if the baseline is negative, and the optimal interval between screens.

Currently screening is either by (1) contrast echocardiography with follow up of individuals with a grade II-IV result, or (2) directly performing a CTPA.

Screening for BAVMs
BAVMs are often asymptomatic, but can present with haemorrhage or epilepsy. There is currently no evidence to support routine MRI brain screening in asymptomatic adults affected with HHT. The ARUBA trial shows that in the short-term the outcomes of unruptured BAVMs are better if left untreated. However, this trial did not include patients with HHT and also longer-term follow up is required to determine if the outcomes differ.[3] Where a patient is symptomatic or is known to have a BAVM, there should be consideration of referral to a specialist neurosurgical clinic.

Antibiotics
There is no clear consensus for the prescription of antibiotics to cover episodes of bacteraemia. In the absence of evidence to the contrary, and given the severity of the potential complications, antibiotic prophylaxis should be considered, at the discretion of the clinician performing the procedure.

Anaemia
Anaemia is a clear risk in HHT. Monitoring for and management of anaemia should be initially in primary care, with involvement of haematology in refractory cases.

Diagnostic testing for HHT
Screening for Hepatic AVMs for the purposes of diagnosis is unlikely to be helpful.
Generally, the most useful adjunct to clinical diagnosis of HHT is mutation analysis of *ENG*, *ALK1* and *SMAD4* genes. Some families may have a mutation in the endoglin promoter region or another gene (e.g. *BMP9*) which are not currently routinely tested. An adult who does not fulfill the Curacao clinical criteria and with no HHT gene mutation identified should prompt reconsideration of the diagnosis.

Future areas of research

It is clear that current evidence to guide practice is limited. A better understanding of the natural history of the disease is needed, especially the incidence of symptomatic PAVMs and BAVMs in children and the evolution of PAVMs in adults.

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Conference report: ESHG conference Glasgow 2015

Hannah Titheradge, ST6 Clinical Genetics

I would like to thank the Clinical Genetics Society (CGS) for enabling me to attend the European Society of Human Genetics (ESHG) conference this year in Glasgow. I am currently doing an MD looking at the application of next generation sequencing (NGS) into clinical genetics. I was able to present a poster on an interesting family from my project with a severe auto-inflammatory disease similar to Weber Christian disease in the hope of identifying other similar families.

There were many very relevant talks at ESHG. I particularly found the bioinformatics online tools created by Peter Robinson and his team to aid the clinical geneticist extremely useful. This talk described many tools including the Exomiser and PhenIX, which both use inputted phenotypic data to aid variant identification from Whole Exome Sequencing (WES). In addition, his workshop on bioinformatics provided a clear overview of the processes needed to interpret WES results. Listening to the experience of several European experts when using NGS was also very illuminating and really emphasised for me the importance of having good phenotyping prior to performing NGS to aid interpretation of the results.

There were a number of sessions not directly related to my MD project that I found extremely informative. The educational session on imprinting-related disorders given by Professor Karen Temple and Professor M Bartolomei provided a concise overview of these disorders and the underlying mechanism involved. I was also very interested to hear how exon skipping to correct the number of cysteines in NOTCH3 could work as a potential therapeutic option based on the mouse work by JW Rutten, one of the winners of the young investigators award.

I was also fascinated to hear the ESHG Award Lecture by Professor Svante Pääbo from the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany discussing his work sequencing the genome of our evolutionary relative, the Neanderthals. We also heard about another group of extinct early humans, the Denisovans. It was very interesting to hear how he was able to use their genomes to piece together the early history of modern humans.

In addition to the vast learning opportunities ESHG provided, there was also plenty of time to catch up with a number of old friends from other centres and meet new genetic colleagues. The ceilidh at the conference dinner on the Monday evening was a fantastic way to mix with a variety of international colleagues. The evening was kicked off in style by the Scottish dancers demonstrating the traditional dances and continued as many of us tried our hand at emulating them at the ceilidh (with varying degrees of success!). It was a thoroughly fun evening.

Once again I would like to thank CGS for being given the opportunity to attend the ESHG conference, I look forward to attending future events and recommend that for anyone who was not able to attend this year to endeavour to attend the event in Barcelona next year.

Trainee Column

Hannah Titheradge
ST6 Clinical Genetics

This is my final trainee column as your SpR representative on the CGS council. It is with sadness that I step down after my three years in post. I have found it a very valuable experience I am very pleased that we have two keen registrars eager to take up this post in my place. At the time of writing, we are currently undergoing the election for this post, with the result expected to be announced in mid-June 2015. (*Editor – Rhoda Akilapa was successfully appointed as the new representative*)

ESHG

It was wonderful to see so many of you at the ESHG conference at Glasgow. Thank you to Mira for arranging an SpR meal on the Sunday evening. It was lovely to catch up with a number of old friends and new alike. Also congratulations to Emma Baple, who has recently left our ranks to become a new consultant in Southampton, for winning the Young Investigators award!

Genome Medicine Masters or PG Cert

We performed a survey of clinical genetics trainees at the end of 2014, asking about your views on the future of clinical genetics. We also asked where you felt the gaps were in your knowledge and current training, to meet these future requirements. Many people wanted to see further bioinformatics and pharmacogenetics training. I thought it would be valuable to summarise the possible options available to meet this need, apologies if this is well known to you.

As part of the 100,000 genomes project, Health Education England (HEE) are running a Master's in Genomic Medicine.

If you meet the eligibility criteria HEE will pay for an individual's course fees for NHS staff. An application for funding is made through HEE's Genomics Education Programme and a separate application should also be made to the individual University for the programme itself.

The content of this course will cover an introduction into human genetics and genomics, Omic technologies, genomics of common and rare inherited disease, cancer genetics, pharmacogenetics, genomics of infectious disease and bioinformatics. This can be done as a full time masters over one year, part time over two years, as a postgraduate certificate (PG Cert) taking a combination of modules equalling 60 credits, or with 120 credits, a postgraduate diploma, and finally individual modules can be taken for Continuous Professional Development or CPD. This course is being run at the University of Birmingham, Newcastle University, University of Manchester, University of Sheffield, Imperial College London, Queen Marys University of London, St Georges Univerity of London, University of Cambridge and the University of Southampton. This is aimed at multidisciplinary NHS healthcare professionals working in England, at the moment. For more information I would suggest you visit **http://www.genomicseducation.hee.nhs.uk/genomicsmsc/**

A PG Cert has been developed by Kate Tatton-Brown and Katy Snape through St George's University of London and is currently being piloted among London Clinical Genetics trainees. This is particularly aimed at Speciality Trainees in Clinical Genetics to understand, interpret and communicate genomic findings through face-to-face teaching, a laboratory attachment, role play and assignments. Discussions are ongoing with the SAC and local centres to see whether this can be rolled out to all trainees. There is a modest fee for this PG Cert.

If you are interested in pursuing a PG Cert or Masters, I would suggest discussing this with your Educational Supervisor and local department. These programmes will require a number of days out of your clinical work to complete the face-to-face training.

Contact details

Please remember to contact Emily Craft with any comments or queries you would like raised at CGS council meetings on emily.craft@uhl-tr.nhs.uk. The contact details of the second SpR representative will be circulated shortly via facebook and the SpR yahoo group.

Save the date

Upcoming meetings for Dysmorphology club

2 December 2015
Institute of Child Health, London

9 March 2016
Cardiff

For more information, please contact: Mhairi.Irvine@gosh.nhs.uk

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Editorial

Helen Hanson

Welcome to the latest edition of the CGG newsletter. In this edition we have an education theme, with a number of articles focussing on the increasing importance of education for Clinical Geneticists. The importance of education in our specialty is bi-fold; we need to ensure we are continuously educating ourselves, particularly in this era of technological advances, but of considerable importance is that as a specialty, we need to engage and provide relevant training for other healthcare professionals.

In our lead article, Diana Eccles and Ellen Copson discuss the growing importance of the need for genetics training for Oncologists. Mainstreaming agendas mean that that in the near future, it is likely that cancer genetics testing will be undertaken in a large proportion of cancer patients directly in the Oncology clinic. However, genetics training has not historically been part of the Oncology training curriculum. Diana and Ellen highlight the reasons why an appreciation and understanding of Genetics is important for Oncologists and highlight areas which need to be addressed in the Oncology curriculum. An interesting point also made in the article is that conversely Oncology training is not a mandatory requirement in the Clinical Genetics curriculum. Modernised medical training means that many trainees may not have had exposure to Oncology clinics in posts prior to Specialist Training. Perhaps with the increasing knowledge of the impact of an individual's genetic status on their cancer treatment, for example the use of platinum chemotherapy or PARPi for BRCA carriers, or how genetic status may affect prognosis, such as poorer prognosis for *BRCA2* carriers with prostate cancer, we should consider how training and education between the specialties could be reciprocated.

In the next article, Katie Snape and Kate Tatton Brown discuss the excellent educational initiatives they have undertaken at St Georges to address the gap in knowledge the genomics revolution has brought for many clinicians – both Geneticists and non-Geneticists. Recognising the multiple levels of complexity that the genomic era has brought, in terms of understanding the new technologies, interpreting the data and finally communicating the data and results to both other professionals and the patient, they have developed an innovative PGcert to provide a genomics education package to ensure that geneticists can feel confident as new technologies become integrated into clinical practice. The PGcert was launched to PanThames trainees last year, but following much interest will be rolled out further in the near future. Recognising that it is not only Geneticists who require training but also the wider healthcare profession, they have also developed a MOOC (Massive Open Online Course), launched in June to educate healthcare professionals about the impact of genomic technologies on their practice. I am sure this will prove to be very popular.

Kate and Katie's use of the internet to deliver genetics teaching to a wider audience demonstrates that even for the most basic and fundamental principles of genetics, the days of textbooks as a standard teaching modality are probably long behind us. However, most of us are probably quite slow to embrace modern technology as a teaching tool. It is for this reason, I found our next article by Professor Sue Clarke very exciting. Professor Clarke introduces the Polyposis app, developed at St Marks, which will have us all reaching for our phones and tablets in clinic. As a profession I think we have been slow to recognise the utility of apps in clinical practice. However, the polyposis app shows how an app can be put to effective use in a clinical setting. I am sure there are many other protocols which could be developed in this way.

Continuing the education theme, in the next article Gillian Crawford discusses her experience of taking a side step from her role as a genetic counsellor to further educate herself and take on a new challenge. Even in the face of writing up, Gillian's article is upbeat and enlightening about her research experience as an NIHR fellow and will hopefully encourage more individuals to consider a period of research.

Next, we have an article from the successful Oncogenetics team at RMH/ICR updating us on new prostate cancer studies, for which you may have eligible patients.

Finally, Ian Frayling hot off the back of the InSIGHT conference in Brazil provides us with a synopsis of the meeting with many new points of interest for colorectal cancer genetics.

I do hope you enjoy the edition, please make a note of future important dates and if you have any suggestions for future articles or any feedback please let either me or Muna know.

Current approaches to genetic education for oncologists

Professor Diana Eccles[1,2] and Ellen Copson [1,3]
[1]Cancer Sciences Academic Unit, Faculty of Medicine, University of Southampton
[2]Wessex Clinical Genetics Service
[3]Southampton General Hospital

In 2001 the Secretary of State for Health noted that the NHS needed to 'change and adapt its services' to meet the challenge of genomics. Over the intervening years, and escalating rapidly, technological advances have enhanced opportunities for research in both tumour and germline genetics which has revolutionised our understanding of cancer biology. Not least of these advances has been the provision of novel targeted anticancer drugs. Detailed genomic analysis of tumours is now not only possible but is an increasingly cost effective part of modern oncological management. The increasing role of genomic medicine in routine care and the need for medical specialities to adapt training and working practices to ensure that patients receive optimal benefit from these advances has been highlighted in the PHG report *Genetics and mainstream medicine: Service development and integration*.[1]

The feasibility of large scale tumour genomic testing within the NHS was demonstrated by the success of the first phase of the Cancer Research UK Stratified Medicine Programme (SMP).[2] Tumour samples (9000) were transferred to three central laboratories for DNA extraction and sequencing on a targeted panel during a two year pilot study. Patient support was clear as 10,750 patients consented to participate, with a consent rate consistently in excess of 95% of those approached to participate. The 100k Genomes Project is now aiming to sequence matched tumour and blood samples from a large cohort of cancer patients.[3] Unlike the SMP projects, verified actionable findings, including inherited cancer predisposition genes will be reported back to the patients' medical team with the potential in some cases to influence care, with the additional challenge of ensuring that findings are fully understood by health care professionals and the implications accurately represented to the receiving patients.

The Association of Cancer Physicians (ACP) is acutely aware of the training needs for medical oncologists that this revolution in genomic medicine brings. In their recently published document *Strategy For Improving Services and Outcomes for Cancer Patients* the ACP recognised the importance of the work of organisations such as the Royal College of Pathologists, the Cancer Research UK Experimental Medicine Centres molecular pathology working groups, the Association of Clinical Pathologists molecular pathology committee and National External Quality Assurance Scheme for molecular pathology in establishing sample handling standards, performance indicators and reporting nomenclature for solid tumour somatic genetic analysis. In addition they seek to promote the concept of standardised research consent for acquiring prospective and enduring patient consent for research use of tissue in routine NHS practice, based on national ethical standards for consent and information. The development of novel designs for clinical trials across multiple tumour sites will see patients stratified by tumour molecular pathology features rather than by organ of origin or histological subtype.

Hitherto in the UK, genetic testing for germline susceptibility has been largely the province of the regional genetics centres to deliver using a model initially based on presymptomatic testing in Huntington's Disease where no intervention was available to ameliorate the disease progression.

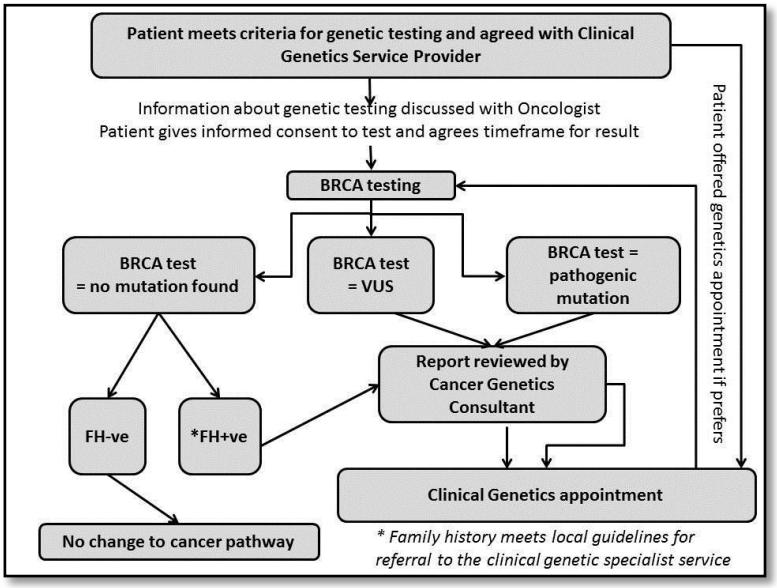
The delivery of cancer genetic susceptibility testing has evolved in most centres but is still not able in many areas to accommodate a rapid referral track for patients with a specific sub-type of cancer but no family history. Changes in the genetic testing guidelines issued in the updated NICE guidelines on familial breast cancer promote a lower threshold of probability for genetic testing.[4] There are several factors that make mainstream testing of cancer patients for cancer predisposition genes (CPG) a more efficient approach to identifying high risk gene carriers. From the cancer genetics clinic perspective, the best starting point for establishing the genetic factors underlying cancer risk is a DNA sample from a cancer affected family member, referral of high risk patients who have not had cancer can complicate and delay the process of identifying a high risk gene mutation; the effective use of the PARP inhibitor Olaparib to treat *BRCA* gene carriers with relapsed ovarian cancer has led to the licensing of this drug for this indication in Europe making the germline genetic testing for *BRCA* mutations relevant to treatment and clinical trials of PARP inhibitors in adjuvant ovarian cancer and both adjuvant and metastatic breast cancer are ongoing.

The role of oncologists in germline genetic testing in order to guide their treatment strategies is clearly recognised by the ACP, their strategy for education recognises and supports the work of the UK Genetic Testing Network Evaluation Group for germline genetic testing. An 'oncogenetic' model of CPG testing, where testing in patients with cancer is performed through the cancer team, with support as required from genetics, is currently being piloted at several sites.

Genetic education for oncologists *cont…*

The Royal Marsden hospital *Mainstreaming Cancer Genetics (MCG) programme* (www.mcgprogramme.com) pioneered this approach and uses online teaching modules to train oncologists to inform and consent selected patients with ovarian and breast cancer for *BRCA* mutation testing. The associated materials can (and should) be adapted for local use and local referral pathways agreed.

Unlike a somatic mutation, identification of a CPG germline mutation has implications for an entire network of relatives and not just for an individual. For a recently diagnosed cancer patient, struggling with cancer treatment and decisions around that, the added concern that they may have 'passed' on a pathogenic mutation to a child may be particularly distressing. It is therefore vital that appropriate and rapidly accessible support is available for patients who receive a positive mutation result. Patients with a negative *BRCA* result but very strong or complex family history will also still potentially benefit from a formal genetics review. The flow chart illustrates a suggested pathway for cancer patients offered genetic testing within mainstream oncology. Patients could choose to have a formal genetics appointment for pre-test counselling in this example and all patients with a mutation or a complex family history would be offered a genetics clinic appointment automatically.



Although the current medical oncology syllabus includes an appreciation of basic aspects of genomic medicine, exposure of oncologists to clinical experience in cancer genetics is currently variable and frequently limited to out-of programme projects. The ACP has established an oncogenetic training working party (OGWP) in order to standardise and enhance the training of medical oncologists in oncogenetics to ensure that medical oncologists of the future are well placed to deal with the rapid advances in cancer genetics and mainstreaming genetics agenda. The OGWP has proposed four potential levels of oncogenetics training:

a) A comprehensive understanding of basic genomics, including limitations of current technology, key differences between somatic and germline mutations and principles of stratified cancer medicine to be mandatory for all medical oncology trainees. The training syllabus for medical oncology is being revised currently to deliver this additional training.

b) Practical experience in cancer genetics clinics as an optional module

c) More advanced experience in oncogenetics provided by formal post CCT cancer genetics fellowships at a small number of tertiary centres for trainees who would like to develop a specialist interest in oncogenetics.

d) Dual accreditation in medical oncology and clinical genetics to be supported for appropriate trainees

As part of the ACP curriculum development work, a survey about training in cancer and genetics was sent to both medical oncology and clinical genetics training programme directors (TPDs). Responses from oncology TPDs in essence indicated that across the UK it is uncommon for medical oncology trainees to be given the opportunity to spend any time in cancer genetics clinics. Responses from clinical genetics TPDs indicated that in a few areas genetics trainees were encouraged to attend some oncology clinics but some responses indicated that TPDs perhaps thought this was not likely to provide a useful experience.

As providers of cancer genetics services, we need to work closely with oncology services to cement close links and implement new pathways. In addition we need to maintain a constructive two way dialogue with our diagnostic laboratory colleagues to support uniformity in reporting to oncologists to minimise difficulties created by uncertain results. We need to provide a united multidisciplinary front to paint a picture of the shape of future services in the wake of this genomic medicine revolution so that the case for adequate resourcing to those that commission our clinical and laboratory services can be made clear and compelling.

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Educating the medical workforce for a genomics era

Dr Katie Snape and Dr Kate Tatton-Brown
St George's University Hospitals NHS Foundation Trust, St George's University of London

"By unlocking the power of DNA data, the NHS will lead the global race for better tests, better drugs and above all better care."
David Cameron, quoted in the Guardian 10 December 2012
"DNA of 100,000 people to be mapped for NHS"

We are in the midst of a genomics revolution. Powerful new genomic sequencing technologies are transforming medicine and allowing speedier, cheaper and more sensitive diagnosis of rare genetic disorders. In addition, these genomic technologies are increasingly being used in the prevention and management of common multifactorial disease; treating and tracking infectious disease and in providing management programmes tailored to an individual's unique genetic makeup.

The 100,000 Genome Project is launching with the involvement of most Clinical Genetics units throughout England as members of Genomic Medicine Centres (GMCs). Through the sequencing of 100,000 genomes from patients and parents with rare genetic disease and paired tumour / lymphocyte samples from cancer patients, the project aims to transform how genomics is used within the NHS, driving genome-directed diagnosis and therapy into the mainstream setting; promote scientific discovery and kick start a UK genomics industry.

However, although the times we live and work in are undoubtedly exciting, genomic technologies are associated with some very real challenges. How will we store the huge volume of data generated? What do we do about incidental findings? How do we determine whether a variant is clinically actionable or not? What should patients be informed of and consented for prior to genomic testing?

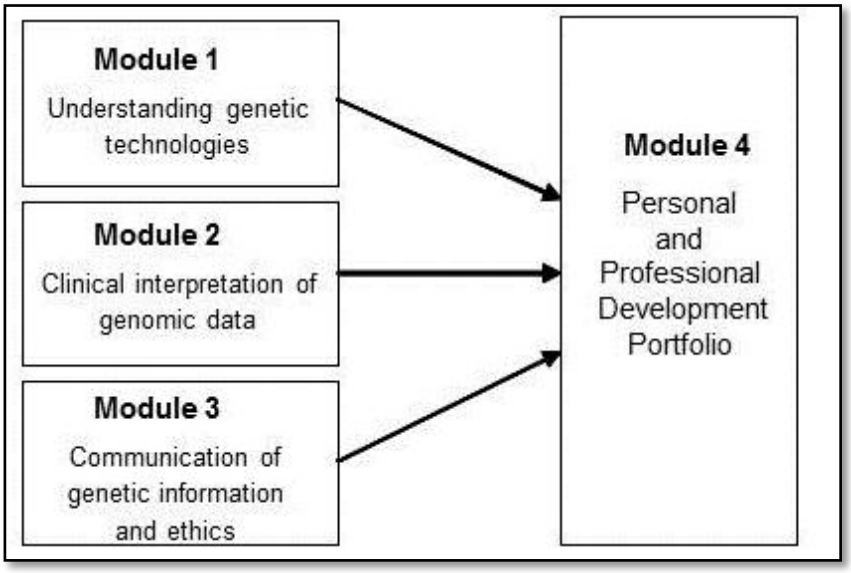

Figure 1 – Modular outline of PGCert ICAG

Genomic education, at both pre and postgraduate levels, is currently limited, leaving clinicians unprepared for this genomics era. At St George's, in collaboration with the Pan Thames Genetics Centres, we sought to address this need by developing a broad genomics education package to: train a specialist Clinical Genetics workforce (Postgraduate Certificate in the Interpretation and Clinical Application of Genomic Data, PGCert ICAG); upskill the non-genetic clinical workforce (a Massive Open Online Course, MOOC); and, in line with other centres in England, provide higher level genomics education through a Health Education England supported MSc in Genomic Medicine.

The PGCert ICAG for Clinical Geneticists in training is a flagship NHS / University partnership, which launched to Pan Thames trainees in September 2014. It consists of four modules which are firmly embedded in the Clinical Genetics training pathway; utilising but restructuring some aspects of the training, thus reducing resources, making it specifically tailored to Clinical Genetics trainees and reducing the amount of extra work the trainees are required to complete. The modular structure of the course is shown in Figure 1. The course aims to enable all clinical genetics trainees to feel proficient in the interpretation of genomic data, and importantly, confident in making clinical management decisions on the basis of their interpretation. We are currently working to deliver module 1 as an online teaching resource to enable the wider dissemination of the programme nationally.

The MOOC was developed in order to address the need for the entire clinical workforce to become competent in integrating genomic data into their clinical practice. In order to achieve NHS-wide education, we required an engaging, easily accessible resource.

Educating the workforce for a genomics era *cont…*

Over recent years MOOCs have become increasingly popular as a means of delivering online education to a wide audience using a variety of media and underpinned by active discussion forums. We have therefore partnered with FutureLearn, the leading MOOC provider within the UK, and, in collaboration with Health Education England, have developed *The Genomic Era: The Future of Genetics in Medicine* (Table 1).

Week	Contents
1 - DNA, the code of life, and the human genome	The fundamentals of genomics; DNA, genes, chromosomes, transcription, translation, cell division, normal genetic variation
2 - When things go wrong with our genes and chromosomes	The introduction of error into the genetic code, inheritance patterns, patient experiences
3 - The changing genomic landscape	Genomic technologies, both cytogenetic and molecular, and understanding genetic reports
4 - Genomic data in clinical practice	The clinical applications of genomic technologies across medical specialities – rare diseases, common diseases, prenatal, infectious diseases, personalised medicine and pharmacogenomics
5 - Ethical considerations and communication skills in a genomic era	Ethical and communication principles, including incidental findings, presymptomatic and prenatal testing.

Table 1 – The structure of the MOOC "The Genomic Era: The Future of Genetics in Medicine".

The MOOC aims to educate healthcare professionals about the impact of genomic technologies on their clinical practice, the issues which need to be considered prior to genomic testing, the complexities associated with the interpretation of genomic variation and the importance of specialist clinical genetics referral where appropriate.

The MOOC launched on June 15 and will be repeated, with updates, approximately three times per year. https://www.futurelearn.com/courses/the-genomics-era

Questions relating to either the PG cert or MOOC can be emailed to ktatton@sgul.ac.uk or ksnape@sgul.ac.uk

A smartphone app for the management of polyposis syndromes

Professor Sue Clark, Consultant Colorectal Surgeon and Director of the Polyposis Registry, St Mark's Hospital and Adjunct Professor of Surgery, Imperial College London.

The polyposis syndromes are inherited conditions characterised by the formation of multiple large bowel polyps as well as various extracolonic features, and include familial adenomatous polyposis, mutYH associated polyposis, serrated polyposis, juvenile polyposis, Peutz-Jeghers syndrome and Cowden's syndrome.

A number of evidence based guidelines for their clinical management are available in the literature. While these provide the information necessary to care for these patients, they are not suitable for practical use in a clinical setting in their published form. In the past we have produced brief written management protocols for use in the outpatients department and other clinical settings in our institution, but these require reprinting when updated, and may not be to hand when required. We also receive frequent requests from clinicians elsewhere to provide copies, but have no means to alert users when we modify the protocols in the light of new evidence.

A smartphone app is an ideal medium for such clinical algorithms.

Smartphone app *cont…*

Apps can be widely disseminated free of charge, is constantly available to the mobile phone user even in the absence of an internet connection once it has been downloaded, and can easily be updated when guidelines change. An additional advantage is that there can be some interactive functionality.

We worked with an app developer to convert our management protocols for the polyposis syndromes into app form (Figure 1 and 2). This includes an interactive Spigelman stage calculator, in which the user selects the appropriate number, size and histology of duodenal adenomas, and the Spigelman stage is automatically calculated. The appropriate management recommendations for that stage are then displayed (Figure 3).

The app was initially piloted by the clinical staff at St Mark's Hospital, and formal feedback obtained using a questionnaire. The resulting information was used to refine the app, which is now available free of charge for iPhones on the 'App Store' and for Android devices via 'Google Play' (Figure 4). In order to publicise the app we submitted information on it to various professional meetings where it was presented in poster form. Currently we are requesting potential users to register, allowing us to capture their contact details before they can use the app. While this means that it cannot be used immediately, this approach will allow us to seek further feedback before upgrading the app, and to inform all users when an upgrade is available.

Our aim is to provide evidence based guidelines for the clinical management of polyposis syndromes in a user friendly readily accessible form, which can be easily updated. The current app has plenty of room for improvement, and we welcome users to 'test drive' it and provide feedback so that it can be improved.

Figure 1

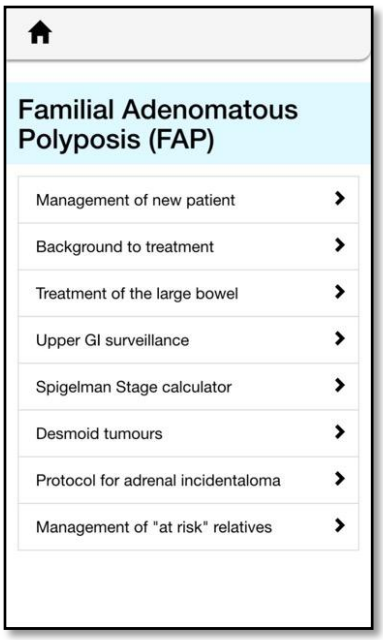

Figure 2

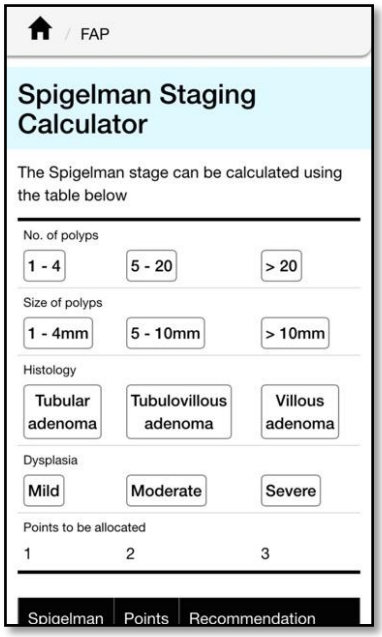

Figure 3

Figure 4

A Clinical Academic Fellowship with the NIHR: the experience of one genetic counsellor

Gillian Crawford,
Principal Genetic Counsellor/Research Fellow
Wessex Clinical Genetics Service/University of Southampton

After working in a post that combined genetic counselling and research for over ten years I was looking for a new challenge. I had been thinking about a PhD for some time but my interest was sparked when I read about the NIHR Clinical Academic Training (CAT) fellowships. Here was a route in which I could develop my research interests and at the same time enhance my clinical skills. I decided to go for it. I developed a research proposal to explore the issue of incidental findings (IFs) from genetic tests (summarised here: www.soton.ac.uk/cels), visited Leeds for a nerve wracking interview, had an extraordinarily long wait for the results (funding decision post last general election had to be made) but a year after applying I began.

Many of us work as clinicians and as part of our role we regularly discuss research studies with families. In clinical genetics the boundary between clinical and a research activity is perhaps less distinct than in other specialities. Genetic testing for a suspected condition may only be available through participation in a research study. As in many areas of medicine we are clinicians with a research remit. How would it be to be a researcher first and foremost? I was about to find out.

Being a researcher in the specialty in which you have significant clinical experience brings its challenges. On one hand your research questions are informed, you have identified issues in practice that need research, you know how the NHS works, how to access your research cohort and you can predict some of problems that may arise. These factors all help as you plan your research. But how much conjecture do you bring, what is the impact of being from the same profession as potential research subjects and do peers modify their behaviour when participating in your research? This last point was one that I needed to address early on in my research during clinic observations with colleagues who were talking with patients about the potential for IFs being discovered with routine genetic testing. I believed that some of the discussions I was observing may not reflect usual practice. Clinicians were explaining about the possibility of IFs and at the same time telling patients that this was the subject of my research, suggesting that perhaps my presence had alerted them to the issue of IFs. This suspicion was confirmed on one occasion when a participant said to their patient that this [a discussion about IFs] was more than they would normally say! Clearly I was affecting their practice and I needed to take this into account when analysing the data.

I also interviewed ‘patients’ who were research participants, for whom I did not have any clinical responsibility. When clinical questions arose during interviews, was I to respond to them? I knew I could, but that was not my role at that time. I had to decide where to draw the line; brief clarifications I decided were ok but anything that warranted discussion or indicated that the patient had misunderstood the information they had been given needed a separate clinic appointment. This made me think about how I presented myself to participants and as the research progressed I became more reticent at revealing that I was a genetic counsellor. This took some adjustment as I was very comfortable in a genetic counselling role but revealing this was neither beneficial to the patient whose clinical expectations would not be met nor me whose research needs would not be met.

Despite all this, it was a luxury it was to be able to focus on research full time, to be able to address this work with continuity and without interruption and to be supported by training and supervision. There were clinical developments during this time in partnership with my research, for example, activities within the Genethics forum.

So would I recommend a move out of clinical work (albeit temporarily) into the world of research and academia? Perhaps now is not the best time to ask as my submission deadline looms and I am grappling with writing, but overall it has to be a big yes! Being enabled to focus totally on research adds so much, you learn new skills along the way, try out research methods you have never performed before and face challenges that scare you but reward you (an appearance on BBC breakfast comes to mind!). This is all with fantastic support, locally from supervisors, university and clinical department and nationally from the NIHR.

NIHR has career pathways supporting clinical academics all the way through, check out their many opportunities on: www.nihr.ac.uk and send me an email (gc@soton.ac.uk) if I can help you decide whether this might be for you.

The latest in prostate cancer genetic research

Dr Liz Bancroft [1,2] , Sibel Saya[2] and Professor Ros Eeles[1,2]
[1]The Royal Marsden NHS Foundation Trust
[2]The Institute of Cancer Research

The Oncogenetics Team at The Institute of Cancer Research has recently opened two new NCRN studies evaluating the role of genetics in prostate cancer (PrCa) risk and targeted screening programmes. We would be interested in hearing from you if you have eligible patients, or you are interested in becoming a study site/participant identification centre (PIC) (Please note that if you become a PIC then the NCRN accrual is allocated to you for any patients who proceed to join the study.). The team can be contacted on 0208 722 4483 or prostate.research@icr.ac.uk.

1. The PROFILE Study: Germline genetic profiling: correlation with targeted prostate cancer screening and treatment

UKCRN ID 16408; MREC No 13/LO/1787

The aim of this study is to evaluate targeted screening for PrCa in men at genetically higher risk. We aim to estimate the incidence of cancer, the sensitivity and specificity of PSA screening in these populations and correlate this with SNP profiles and biological endpoints. Additionally the study aims to identify serum and/or urine markers (for example PRCA3, hK2 and free: total PSA ratio) and imaging technologies (e.g. MRI and new imaging techniques) predictive of the risk of developing PrCa and to correlate these with genetic risk.

A pilot study at The Royal Marsden NHS Foundation Trust in London recruited 100 men from the target population and demonstrated the feasibility of the study. The study has now been extended with the aim of recruiting 350 Caucasian men with a family history of PrCa and 350 men of black African or black Caribbean ancestry irrespective of family history.

All men are offered a MRI and trans-rectal ultrasound guided prostate biopsy. A DNA sample is taken for genetic analysis and a polygenic risk score based on a panel of ~100 SNPs will be reported back to the patients. All men in the study will be followed up with 6 monthly PSA readings for 5 years and re-biopsied if their PSA rises > 50%. Those diagnosed with PrCa through taking part in the study will be referred to their local centre for standard NHS treatment.

Eligibility:

- Men aged between 40-69 years of black African or black Caribbean descent (with 4 grandparents of that origin)

OR

- Caucasian men aged between 40-69 years with a family history of PrCa defined as:
    - Men with a first degree relative with PrCa diagnosed at <70 years
    - Men with two relatives on the same side of the family diagnosed with PrCa where at least one is diagnosed at <70 years
    - Men with three relatives on the same side of the family with PrCa diagnosed at any age

Exclusion criteria

- Previous cancer with a life-expectancy of less than five years
- Previous PrCa
- Negative biopsy within one year before recruitment
- Contraindications to MRI and/or prostate biopsy

The PROFILE study is funded by Movember and PCUK and Cancer Research UK

2. GENPROS: Analysing outcomes after prostate cancer diagnosis and treatment in carriers of rare germline mutation in cancer predisposition genes

UKCRN ID 16332; MREC No 14/LO/0072

The GENPROS study aims to observe PrCa outcomes in patients with rare germline genetic variants including *BRCA1*, *BRCA2*, and Mis-Match Repair gene mutation carriers and who have been diagnosed with PrCa. In this first phase of the study (the *BRCA* phase) we are aiming to recruit 150 *BRCA1* mutation carriers with PrCa, 105 *BRCA2* mutation carriers with PrCa and 765 controls (men with PrCa who have tested negative for *BRCA1* and *BRCA2* mutations).

We aim to investigate whether PrCa patients who carry a rare germline mutation have (i) a shorter Cause Specific Survival (CSS) compared with non-carriers; (ii) a shorter biochemical progression free survival and metastasis free survival after radical treatment for PrCa than non-carriers (iii) evaluate progression free survival and CSS from metastasis. The study will also use genetic profiling to investigate whether common allele profiles or specific common alleles, also have an association with prognosis and treatment outcome.

Men who consent to take part in the study will be asked to provide a DNA sample (saliva or blood) as well as give permission for access to their medical records and pathology samples. Recruiting centres will be asked to complete a short treatment questionnaire on an annual basis for each participant.

The latest in prostate cancer genetic research cont…

This study is covered under the Musketeers' Memorandum and so all regional genetics services are signed up to take part.

Inclusion criteria:

- Men diagnosed with PrCa at any age are eligible for the study if they are either:
  - A known carrier of a *BRCA1* or *BRCA2* mutation OR
  - A known non-carrier of a *BRCA1/2* mutation.

The GENPROS study is funded by Cancer Research UK

InSiGHT Conference 18-20 June 2015, Sao Paulo, Brazil

Dr Ian M. Frayling
Consultant Genetic Pathologist, All-Wales Medical Genetics Service

With the generous support of CGG I have been able to attend this meeting as a member of the InSiGHT faculty. The significance and depth of all the findings and data presented have been and will be considerable. I write this the day after and the dust is still settling, but here, in rough order of their presentation are some items of interest. The points made may be compiled from more than one piece of work presented. Opinions, errors, omissions etc are all mine.

- The abstracts are publicly available at **http://www.2015insight.com/wp-content/uploads/2015/06/2015-Insight-abstracts-1.pdf**

Vaccination of Lynch patients with both monocyte-derived dendritic cells and specific frame-shift peptides (FSP) is showing great promise. These are safe and lead the way to trials of prophylaxis. The vaccine Micoryx induces the strongest T-cell mediated immune responses yet seen in an anti-cancer vaccine. LS patients' colorectums have of the order of ~100,000 abnormal MMR-deficient crypts, potential pre-malignant lesions – these are continually autoimmunising LS patients against FSPs. In addition, these early mono-cryptal events lead to more advanced submucosal lesions, because they acquire mutations in beta-catenin rather than *APC*. However, this is associated with a reduced propensity to metastasis. Hence, it is proposed that this may be the reason colonoscopic surveillance in LS (presented elsewhere in the conference) reduces mortality from CRC by downstaging, but does not reduce the incidence of CRCs themselves, moreover regardless of the number of adenomas removed. All rather heretical, until one realises that the assumption CRCs in LS all arise from adenomas, a la FAP, has been an assumption too far.

The only actual data that has been published on the efficacy of colonoscopy in LS (the famous 'Finnish data') is on the effect of 3-yearly colonoscopy. The assumption has been made, by extension from screening in the general population, that as colonoscopy prevents CRC, so more colonoscopy must be better in LS. Data from the prospective InSiGHT Europe co-ordinated LS database is, however, showing that while colonoscopy definitely reduces mortality, it is not related to adenoma removal, rather the effect is by downstaging of the cancers. Moreover, an interval of 3 years between 'scopes is adequate, which will come as a relief to many. In addition, excellent Dutch data on colonoscopic surveillance of those at moderate risk of CRC, outside of LS, indicates that a 6 yearly interval in such situations is entirely satisfactory. Hence, we have better and increasing evidence that colonoscopic surveillance works, although not in LS in a way we might have thought, and future demands on colonoscopy services may not be as great as are feared.

A major and important piece of work from the Colon Cancer Family Register was presented by Aung Ko Win on lifestyle and personal history factors in LS. This is due to be published imminently in JCO. We can help LS patients with surveillance and surgery, but this will provide the opportunity for other interventions, some of which patients themselves have the option of adopting.

InSiGHT Conference *cont…*

All the following have significantly raised/lowered HRs:-

- Being a current smoker confers an HR of 1.62, whereas in former smokers the HR is 0.53. So, advice on smoking in LS is clear.
- The HR per 5 kg/m^2 BMI is 1.30, so advice on maintaining a healthy weight is clear.
- As in the general population, beer/cider consumption is associated with rectal cancer, the HR for rectal cancer and beer/cider consumption in LS being 1.19 per 14 g unit of alcohol per day. However, for colon cancer in LS the HR is 1.34, but only with spirits.
- Aspirin use up to 5 y has an HR of 0.49, while >5 y it is 0.25. Proof, if ever it was needed, of the need to do CaPP3. For Ibuprofen use the corresponding figures are 0.38 and 0.26, so aspirin is not the only NSAID that has an effect, and it may thus be an option in those who cannot tolerate aspirin. [It is also worth bearing in mind that 50,000 colonoscopies will cause three deaths, whereas *perhaps* one death due to aspirin will occur in 50,000 individuals treated over a 3 year period – and many deaths due to other causes will be prevented by the aspirin.]
- Multivitamin use up to 3 y has an HR of 0.59, and >5 y it is 0.45. Similarly, calcium supplementation has corresponding HRs of 0.50 and 0.40, but for folate there is no effect either up or down. [There have been concerns folate might increase CRC risk.]
- Oestrogen-only HRT has no effect, but combined oestrogen and progestin HRT for ≥6 months has an HR of 0.23. However, OCP use makes no difference.
- Parity confers an HR of 0.50, but the effect is only seen in women who have given birth twice (HR 0.43) or three or more times (0.37), providing extra evidence for an effect of progestins.

Evidence was presented from the USA on the utility of systematic testing of CRCs to identify LS, backing up work in the UK, Denmark and elsewhere. Whereas those in the USA reckon it would be worth it to screen all CRCs, the evidence from Europe (with a much different health economy) is that >70 y it is not worth it and resources would be better allocated elsewhere.

Professor Achatz gave a fascinating talk on Li-Fraumeni syndrome and the associated young–onset GI cancers, both upper and lower GI tract. About ¼ of all identified LFS families on the planet are in Brazil, and this is due to a strong founder effect. Indeed, the families are located along the route of a 16th century mission trail from NE to SW Brazil, so it seems one particular priest was not just spreading the word of the church, but also *TP53* R337H!

There was a meeting of the InSiGHT Variant Interpretation Committee at which an in depth discussion took part on definitions such as 'mutation', 'pathogenic', something (anything!) better than 'VUS' etc. This will feed into a wider debate including the HVP and e.g. ENIGMA, subsequent to a retreat held earlier this year under the auspices of Decipher at the Wellcome Trust Sanger Centre on the whole subject of the interpretation of mutations. It is intended that a definitive position statement will be published later this year on this point. The latest set of uninterpreted mutations was also considered, and work will now be ongoing to extend what has been done for MMR to the other genes for which InSiGHT has responsibility (as agreed by the HVP). So, the first of these is *STK11* and Peutz Jeghers syndrome and many will have already been contacted about this. A major issue is data sharing across borders. Usefully, the Royal Melbourne Hospital's clinical ethics committee (the RMH hosts the curator and the database) takes the opinion that not to put clinical mutation data into databases where it may be interpreted for the greater good is contrary to good medical practice. In effect, they are saying it is unethical not to share data, so this opinion will be shared with the agencies in other countries as a way of facilitating such work.

Other points (among many) include:-

- Individually rare loss of function non-recurrent CNVs are revealing novel CRC genes.
- *NTHL1* is identified as a polyposis-associated gene, encoding as it does a counterpart of MUTYH. Also, there were many talks and posters on *POLD1* and *POLE* mutations causing polymerase proof-reading adenomatous polyposis. So, we now have (P)PAP and NAP to add to MAP, FAP and AFAP. PAP and NAP are associated with polyposis (few to maybe a couple of hundred adenomas), but also with Lynch-like tumour spectra. So, this all makes a case for gene panels and to review all those families in the clinic where mutations have not been found in the [up to now] known genes.
- Promising work was presented on macrolide antibiotics as a way of alleviating FAP due to nonsense mutations in *APC*, because such agents facilitate a degree of 'read-through' at such codons.

InSiGHT is a very small charity and provides a great deal in promoting collaborations, issuing guidelines and being world leaders in mutation interpretation. So, I would encourage all those who benefit from this work and who have an interest in the field of GI and related hereditary cancers to consider membership, full details of which can be found at http://insight-group.org/ .

Lastly, the sad death of Professor Richard ('Dick') Cotton was announced at the meeting. Dick was a personal friend, hugely inspirational and a good person. He will be missed. The ESHG have posted an appreciation of Dick and his work (https://www.eshg.org/141.0.html

)

Dates for your diary

Helen Hanson

This year's CGG Winter meeting will be held on Friday 4 December 2015, at the Institute of Neurology, Queens Square, London.

Following the successful joint meeting in Leiden in 2014, there will be a Joint UK/Dutch CGS and CGG meeting held in Cardiff on 7-8 March 2016.

In 2016, the Sixth International Symposium on Hereditary Breast and Ovarian Cancer, *BRCA: Challenges and Opportunities*, will be held at Centre Mont-Royal, Montréal, Canada between May 10-13 2016.

Although it feels like no time has passed since NICE guideline CG164 on Familial Breast Cancer was published in June 2013, it will shortly be reviewed to see if it requires any updates. Please register as a stakeholder via the NICE website if you would like to be informed about the decision (http://www.nice.org.uk/guidance/cg164).

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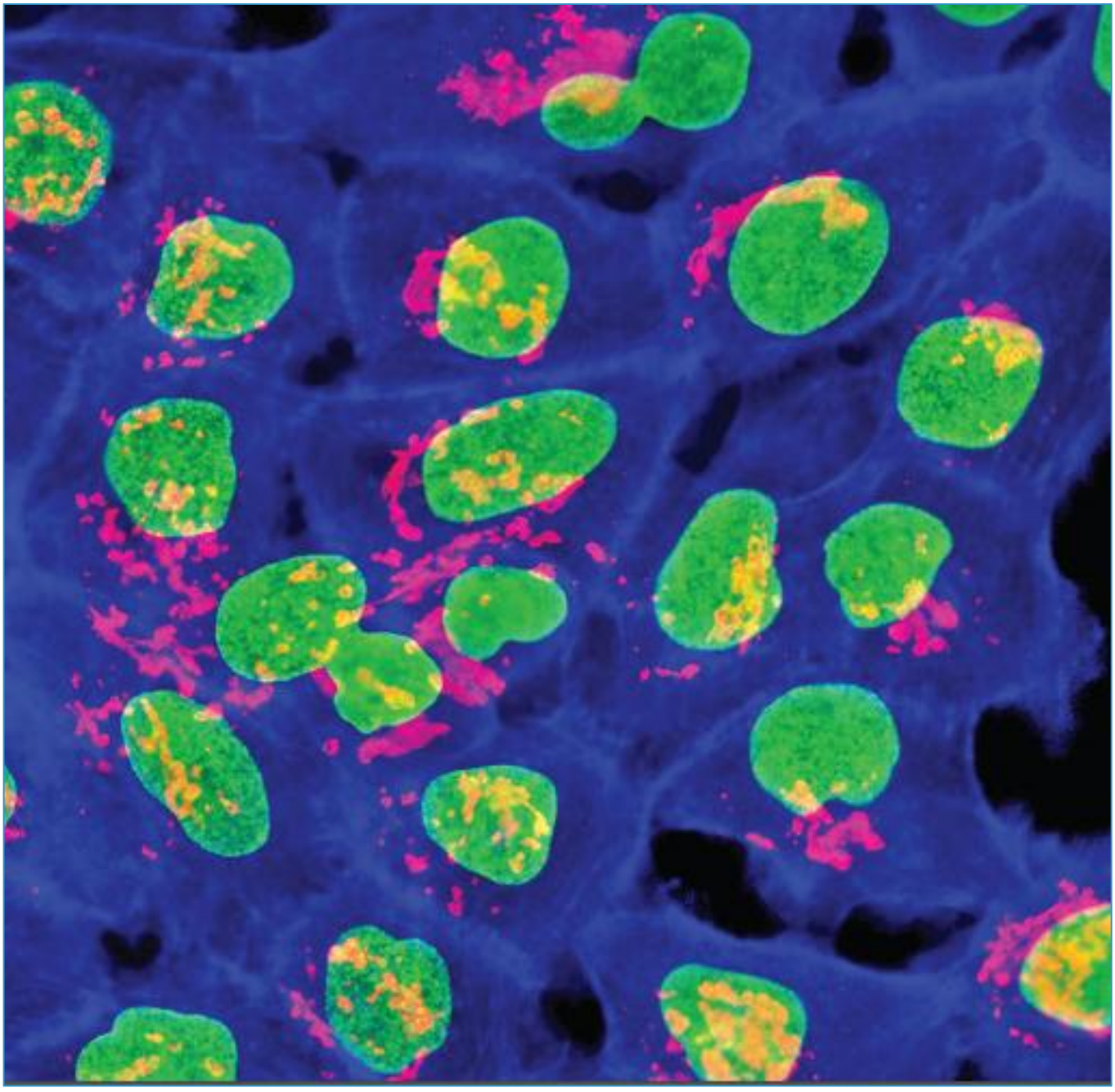

Human Skin Epidermoid Carcinoma Epithelial Cells (A-431) © Michael W Davidson, National High Magnetic Field Laboratory, Florida State University (http://micro.magnet.fsu.edu/primer/techniques/fluorescence/gallery/cells/a431/a431cellslarge.html)