**BSHG News**

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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)
Welcome to this bumper issue of the BSHG News, which contains articles reporting on local initiatives, updates on national projects as well as information regarding international collaborations. This issue also has a slight diversion from the normal format with our Chair, Professor Sir John Burn, providing the lead article. In this article Sir John Burn outlines the aims of the Human Variome Project and how members of the BSHG can contribute to this international project.

As well as numerous articles providing updates on national projects such as DDD and RAPID, this issue also contains six reports on conferences attended by BSHG members, five of which were international meetings. Three of these members were recipients of a BSHG travel award, which contributed to their costs in attending the overseas conference. All BSHG members, as long as they have been a member for at least one year, are eligible to apply for a BSHG travel award. There are four deadlines each year for applications, with the next deadline 1 April 2013. Further deadlines each year for applications, with the next deadline 1 April 2013. Further

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

Michelle Bishop

How to aVoid a Pileup-The Human Variome Project (HVP)

John Burn, Chair BSHG and member of the Scientific Committee, Human Variome Project

It seems like every passing week brings a new revelation in the pursuit of the thousand dollar genome. Even the most pessimistic now recognise that the days of Sanger sequencing as the front line technique in diagnostic molecular genetics are numbered. It will, of course, remain of value as a confirmatory methodology but even this is unlikely to be a long lasting role. So clinicians must adjust to being able to have the sequence of any or all genes on demand while the labs must get used to a world where massive data sets are the norm. The practice of diagnostic laboratory genetics will progressively move away from the bench and towards the computer screen. While all of the above raises major challenges, none are as great or as pressing as the issue of interpretation.

The world record for traffic jams is currently set by a ‘snarl-up’ in China in August of 2010 which was over 100km long and stood still for 11 days, but this is trivial compared to the challenge of making sense of one, two or even three million variants per person as our genomes are sequenced in ever greater depth. In particular, we must work out how to make sense of the millions of missense variants being generated. Some are of pivotal diagnostic importance but most are bystanders or completely irrelevant.

Evolutionary conservation, ribbon maps of proteins, predictive algorithms for gene structure, knock-ins, knock-downs and knock-outs and fiddling with the innards of stem cells will all contribute to our understanding. We will all become familiar with Grantham numbers’ a technique which maps all the variants known at a position in three dimensional space based on physicochemical properties then measures how far away the variant of unknown significance lies from that physiological zone.

But all this takes time and massive laboratory and intellectual resources. We cannot afford the money or time involved in endlessly reinventing the same missense wheel. This is where the Human Variome Project (HVP) enters the arena. Conceived by Dick Cotton in Melbourne almost a decade ago and launched alongside the International Human Genetic Conference in 2006 in Brisbane, the idea was to pick up where the Human Genome Project left off and gather in an accessible format all the variation in humanity. While understanding the pathogenicity of variants in genes of clinical significance is the central driver, such a pool of data would also drive our understanding of complex trait predisposition and with it the intelligent development of new drugs, to say nothing of the prospect of finally making a reality of the promise of pharmacogenetics.

At the time, analysing a genome was still in the ‘going to the moon’ category and the early protagonists were mainly those who had set up successful research databases involving the rare disease of their preference such as the haemoglobinopathies and cystic fibrosis. With the advent of parallel pyrosequencing and its cousins, a new breed of large scale genomicists entered the arena and were somewhat dismissive of the HVP; too small scale, last generation and Australian. But the team pressed on and
have developed a plan to have individual
country nodes linked into a global network
of free access databases. HVP have made
great efforts to emphasise that this umbrella
organisation should be considered with the
linker ‘AND’ not ‘OR’. In the UK the team at
the Wellcome Trust Sanger Institute and the
European Bioinformatics Institute, located at
the Wellcome Trust Genome Campus, are
now focused on the challenge while in the
United States a database called Clinvar is
under development. Thanks to the efforts of
Patrick Willems the large diagnostic labs in
the USA, other than Myriad, have agreed to
download their vast collection of data;
Myriad see commercial benefit in standing
apart and using their BRCA1 and BRCA2
sequence knowledge to retain their
commercial edge. Patrick explored the idea
of a commercial international database to be
called Mutadatabase but has now
concluded that this needs to be set up in the
public sector and supported at an
international level.

Meanwhile, HVP has achieved two major
advances; it is now recognised as an official
partner of UNESCO who will continue to
host its meetings in its Paris headquarters
every 2 years and the Chinese government
have signed up as an official sponsor. In
addition to making available a large number
of bioinformaticians to help run locus specific
databases, the Chinese government have
provided a substantial budget for the HVP
head office in Melbourne allowing meaningful
progress on the international front.

At a major meeting in Beijing in December
2011, HVP succeeded in persuading their
Chinese colleagues to release a million
dollars to set up partnerships between
genetics centres in developed countries and
genetics teams struggling to get started in
developing nations. HVP now has a
presence in 72 countries. The large scale
sequencers have realised the critical
importance of having access to phenotypes
as the role of rare variants becomes more
prominent. The European Union have set up
a new Rare Disease initiative which needs to
be linked into the picture. Moves are afoot to
win World Health Organisation approval and
in general, the train appears to finally be
leaving the station.

What does this all mean for individual
members of the BSHG? Quite a lot is the
answer. If we can develop a trusted single
source of up-to-date and verified variant
data our lives will be a lot easier. But to
achieve this we need all professional
geneticists to get involved. As a proof of
principle, the InSiGHT database now has an
international team of experts discussing new
discoveries in the mismatch repair gene
defects and adding these to the public
database hosted in Leiden on their open
database system, LOVD. I often talk to
diagnostic scientists who tell me that their
new variant is not on that database, yet I
have never met one who then said “so I
sent mine in”. We are all busy and some of
us are faced with obstruction from Trust
managers who wave the shroud of
confidentiality as an excuse for doing
nothing. Andrew Devereau is working
towards transforming the Diagnostic
Mutation Database (DMuDB) developed in
the UK into the country node for HVP. The
key here is to ensure that high quality data is
automatically uploaded. Miles Axton at
Nature Genetics is working on a
microattribution approach such that the
contributor gets something to add to their
CV. This is valuable but we also need a way
of ensuring all the data held by the
diagnostic labs reaches the public domain.

There have been extensive discussions
around the possibility of linking accreditation
to automatic uploading of all variants to a
managed database. As the NHS moves
towards a more integrated genetic
diagnostic service, there is an opportunity
for the British labs to jump before they are
pushed. We can set a deadline by which
time all labs being paid by the NHS must
have developed a means of safely and
consistently uploading ALL variant data
linked to some degree of phenotypic data
into a shared space where it can be subject
to collective analysis. Those who object on
grounds of privacy must be reassured by
rigorous data protection and avoidance of

“What does this all mean for
individual members of the BSHG?
Quite a lot is the answer”
In 2011 a group of British geneticists agreed to launch a new professional association with the aim of supporting and working with genetic professionals from the Indian subcontinent. This group has been actively involved in a number of educational activities under the Indo-UK Genetic Education Forum, including the symposium on clinical dysmorphology Genes and Human Malformations, held in February 2012 in Bangalore and led by Dr Meena Bhatt.

The forum has plans for several educational and professional visits and symposia in India including the following meetings in January 2013:

- Mumbai (Cancer genetics, 23-25 January 2013, led by Professor Shirley Hodgson, London)
- New Delhi (Next generation genetics & genomics, 27-29 January 2013, led by Professor Ishwar Verma, New Delhi)
- Lucknow (Genetic & genomic medicine, 31 January 2013, led by Professor Dhavendra Kumar, Cardiff)

Similar multi-centre symposia are planned across India in 2014 and 2015. Other countries of the Indian subcontinent (Sri Lanka, Bangladesh and Myanmar) have also expressed interest in hosting similar professional events.

The forum has received invitations for hosting genetic and genomic symposia in Asia-Pacific, Africa and Latin America with genetic professional organisations such as the Indian Society of Human Genetics, Asia-Pacific Human Genetic Society, African Society of Human Genetics and Latin American Human Genetics Group expressing an interest in forming a link with the forum. There is therefore a tremendous opportunity for British genetic & genomic professionals to utilise this opportunity and expand their interests overseas. Because of this, several members of the forum now agree that the new association should not be restricted to one geographic region and as such be renamed as the Association of British Geneticists International or ABGI.

The membership of the group is free, voluntary and open to any British genetic professional working in academic, NHS or private sector with an interest to engage with overseas genetic and genomic professionals. Other professionals, such as those working in law, technology, bio-ethics and economics etc. who closely work with genetics or genomics and share similar interests are also most welcome to join.

ABGi members will meet annually on the eve of the BSHG annual conference. At the most recent meeting, held over an informal dinner in Warwick on 17 September 2012, the group unanimously endorsed the proposal to change the name to reflect a broader international remit. The next meeting shall be held in Liverpool in September 2013. Details on venue and time etc. will be communicated through BSHG.

For membership enquiries and information on future professional & educational events, please provide your contact details and professional affiliation/interests via email to

Kumard1@cf.ac.uk or dkumar@glam.ac.uk

You can read more about the HVP at www.humanvariomeproject.org. I look forward to welcoming more of you aboard!

Reference
A new approach to service evaluation in clinical genetics services using a Patient Reported Outcome Measure: Measuring patient benefits

Marion McAllister, Cardiff
Gillian Scott, Glasgow
Sally Watts, Guy’s
Charlotte Eddy, St Georges
Athalie Melville, NW Thames
Charlotte Eddy, St Georges
Sally Watts, Guy’s
Gillian Scott, Glasgow
Marion McAllister, Cardiff
Anita Bruce, GOSH

This article describes pilot studies in Glasgow and London testing a new clinical genetics service evaluation method demonstrating significant measurable patient benefits. Findings suggest that the approach has potential to generate useful evidence for clinical and commissioning decision-makers.

Sandra Tribe, Senior Commissioning Manager, London Specialised Commissioning Group said about the exercise: “The view from the London Specialised Commissioning Group … is that in the past it has been difficult to identify and quantify outcome measures because genetics is either part of an overall treatment pathway or it advises patients on how to manage and live with their genetic condition. As such, outcome measures have not been sophisticated enough to measure their outputs. The ability to identify a range of tailored specific outcomes is welcomed and will enable commissioners to procure high quality and cost effective services which benefit patients so they can make more informed choices about their lifestyle.”

At present, NHS genetics services are not routinely evaluated on the basis of patient benefits delivered. Instead, services are evaluated using process measures e.g. number of genetic tests done, waiting times, numbers of patients attending.

Patient outcomes can be measured using Patient Reported Outcome Measures (PROMs) - short self-completion questionnaires measuring healthcare quality from the patient perspective.1 PROMs have recently taken centre-stage in UK healthcare evaluation, reflecting the NHS quality improvement agenda.1

A new PROM, the Genetic Counselling Outcome Scale (GCOS-24, Fig 1), developed in Manchester, with funding from Department of Health and Medical Research Council, was shown to be valid, reliable and responsive.2 GCOS-24 measures benefits identified by clinical genetics patients and clinicians,3 summarised by the term “empowerment”, which includes:

1. Cognitive control (sense-making): having the best available scientific explanation for what has happened in the family; understanding risks to self/other relatives; knowing what help/support is available.
2. Decisional control: having options for managing the condition/risk and able to make informed decisions between options.
3. Behavioural control: able to use health and social care systems effectively to reduce harm/improve life for self/child(ren)/at risk relatives.
5. Hope: for a fulfilling family life, for oneself/relatives/future descendents.

Patient empowerment is also a key aspect of current UK health policy for improving service quality.

Pilot studies
GCOS-24 was first used to evaluate NHS genetics services in Glasgow by Gillian Scott, as part of her MBA in Public Sector Management (Fig. 2). Following discussions at the South East of England Genetics Network (SEEGEN), attended by clinicians from the four London Centres and the regional commissioners, a pilot project using GCOS-24 was conducted across SEEGEN in 2011-12. The approach involves patients completing GCOS-24 before, and 2-4 weeks after clinic attendance, and measuring group level before-after change in total GCOS-24 scores.

Four centres demonstrated highly statistically significant improvement in GCOS-24 scores following clinic attendance with usable sample sizes of 45 (Glasgow), 54 (Guy's), 55 (NW Thames) and 74 (St Georges), p<0.0001 in all centres. However, insufficient matched pre-clinic and post-clinic questionnaires were obtained at Great Ormond Street to enable a useful analysis (9 matched pairs).

Findings demonstrated that:
- NHS clinical genetics services can deliver significant measurable patient benefits
- GCOS-24 has potential to evaluate routine NHS clinical genetics services

However, GCOS-24 response rates were low in all centres, so not all patients were represented.

Discussion
GCOS-24 service evaluation can supplement traditional service evaluation approaches, to generate patient outcome data useful to decision-makers e.g. commissioners. However, further work is needed to optimise methods prior to implementation in routine NHS practice, in particular to:
- Optimise patient response rates
- Develop systems to match pre-clinic and post-clinic questionnaires, whilst maintaining anonymity
- Explain the exercise to patients: if patients are unclear who should complete GCOS-24 and why, response rates are likely to be low
Using the scale below, circle a number next to each statement to indicate how much you agree with the statement. Please answer all the questions. For questions that are not applicable to you, please choose option 4 (neither agree nor disagree).

<table>
<thead>
<tr>
<th>Statement</th>
<th>1 = strongly disagree</th>
<th>2 = disagree</th>
<th>3 = slightly disagree</th>
<th>4 = neither disagree nor agree</th>
<th>5 = slightly agree</th>
<th>6 = agree</th>
<th>7 = strongly agree</th>
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<tbody>
<tr>
<td>I am clear in my own mind why I am attending the clinical genetics service.</td>
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<td>I can explain what the condition means to people in my family who may need to know.</td>
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<td>I understand the impact of the condition on my child(ren)/any child I may have.</td>
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<td>When I think about the condition in my family, I get upset.</td>
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<td>I don’t know where to go to get the medical help I / my family need(s).</td>
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<td>I can see that good things have come from having this condition in my family.</td>
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<td>I can control how this condition affects my family.</td>
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<td>I feel positive about the future.</td>
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<td>I am able to cope with having this condition in my family.</td>
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<td>I don’t know what could be gained from each of the options available to me.</td>
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<td>Having this condition in my family makes me feel anxious.</td>
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<td>I don’t know if this condition could affect my other relatives (brothers, sisters, aunts, uncles, cousins).</td>
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<td>In relation to the condition in my family, nothing I decide will change the future for my children / any children I might have.</td>
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<td>I understand the reasons why my doctor referred me to the clinical genetics service.</td>
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<td>I know how to get the non-medical help I / my family needs (e.g. educational, financial, social support).</td>
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<td>I can explain what the condition means to people outside my family who may need to know (e.g. teachers, social workers).</td>
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<td>I don’t know what I can do to change how this condition affects me / my children.</td>
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<td>I don’t know who else in my family might be at risk for this condition.</td>
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<td>I am hopeful that my children can look forward to a rewarding family life.</td>
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<td>I am able to make plans for the future.</td>
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<td>I feel guilty because I (might have) passed this condition on to my children.</td>
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<td>I am powerless to do anything about this condition in my family.</td>
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<td>I understand what concerns brought me to the clinical genetics service.</td>
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<td>I can make decisions about the condition that may change my child(ren)’s future / the future of any child(ren) I may have.</td>
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“GCOS-24 was perceived by clinical staff to be easy to use and effective for assessing genetic counselling impact”

Other lessons learned
1. IT systems may enable joint printing of GCOS-24 covering information and appointment letter, for posting with the pre-clinic questionnaire
2. Alternatively, GCOS-24 can be given to patients when they report to reception for their appointment with a request to hand it to the completed questionnaire to their clinician
3. Patient feedback suggested amending covering letters to clarify:
   a. What the exercise is about
   b. Who is being asked to complete GCOS-24 e.g. if the patient is a child, the parent(s) should complete GCOS-24 from their perspective (not from their child’s perspective)
   c. Not all questions are relevant to all patients; for irrelevant questions, the appropriate response is ‘neither agree nor disagree’
4. Post-clinic questionnaires can be given to patients immediately following their appointment for return by post, or sent with the clinic summary letter
5. Administrative support is required to manage the process
6. Hospital audit departments may be able to transfer data electronically into Microsoft Excel
7. Reminder letters can improve response rates

GCOS-24 was perceived by clinical staff to be easy to use and effective for assessing genetic counselling impact, although data analysis requires statistical expertise. In one centre, a small number of families commented that GCOS-24 had caused distress suggesting either that GCOS-24 may not be suitable for all families at first clinic attendance or further explanation would be helpful. This experience indicates that care is needed and obtaining more patient feedback about experiences of completing GCOS-24 may be useful. Individuals attending genetics clinics are often attending due to sensitive issues and may be experiencing significant anxiety, but this may be largely related to the issue about which they are attending rather than caused by the questionnaire. In Glasgow the covering information clarified to patients that if they were upset on completing the questionnaire, they could telephone the genetic counsellor.

Next steps
Marion McAllister is working with experts at Bangor Business School and Swansea University, and with clinical genetics colleagues to develop an implementation plan to address these issues, including automation of GCOS-24 data analysis. Sally Watts is working to optimise GCOS-24 patient response rates under the auspices of the NHS London “Clinicians in Commissioning” course (CASS Business School). We will continue to report progress over time.

References
NIHR Collaborative Group for Genetics in Healthcare – update

Rebecca Hill, Genetics Editor, Progress Educational Trust
James Brooks, Science Editor, Progress Educational Trust
Sarah Norcross, Director, Progress Educational Trust
On behalf of the NIHRCollaborative Group for Genetics in Healthcare

1. Knight champions the need to collaborate

On Monday 17 September 2012, Professor Sir John Burn, Chair of BSHG, told Radio 4’s Today programme “Now is the time for the community of geneticists to get their act together.”

Closer collaboration at a national level is required, he said. The UK has historically been more open than other countries when it comes to genetic science. As such, Sir John says, a “very strong community of professionals” has flourished which is fully able to meet the challenges of the forthcoming years. However, many more geneticists need to get involved if the health benefits promised by the genomic era are to be realised.

In a session entitled Practical Research in Genetic Healthcare, chaired by Sir John at the recent BSHG Conference, delegates learned how the National Institute for Health Research Genetics Speciality Group helps and supports research and facilitates geneticists getting involved.

Alastair Kent, director of Genetic Alliance UK, reminded the audience that families living with a genetic condition were members of a club they didn’t want to join, which they were keen to leave as soon as possible. “They see research as an escape route” he said. “Sometimes this research provides hope for a cure, more likely it will provide a new insight, better management, increased options or just more information.”

Updates were given from three research projects which benefit from NIHR Comprehensive Clinical Research Network support. Dr John Crolla, a lead investigator on the Evaluation of Array Comparative Genomic Hybridisation (CGH) in Prenatal Diagnosis of Fetal Anomalies (EACH) (UKCRN ID 11729) project outlined this multicentre study. The question it seeks to answer is whether prenatal array CGH is more effective than karyotyping in detecting pathogenic copy number variations in fetuses with ultrasound abnormalities. There has been a revolution in postnatal cytogenetics driven by array CGH replacing karyotyping and now that array CGH is set for use in prenatal diagnosis it should have a significant impact, particularly in genetic counselling. Work is being carried out on this project in centres around the country. “It is not too late to get involved”, said Dr Crolla, “but you will need to be self-funded.” All the recruitment criteria can be found on the UK Clinical Research Network’s website (http://public.ukcrn.org.uk).

Dr Helen Firth, consultant clinical geneticist at Addenbrooke’s Hospital compared setting up and running the Deciphering Developmental Disorders (DDD) (UKCRN 9955) project to organising and coordinating the Olympic Games. The ambitious project, which aims to study the genomic basis of severe developmental disorders to improve their diagnosis and management, involves doctors in 23 NHS Regional Genetics Services throughout the UK. DDD aims to recruit 12,000 participants. For that the project needs every consultant to recruit just three patients per month for the three remaining years. Just as the games-makers were key to the success of the Olympics, the genetics community needs to play its part and get behind the DDD project, she said. “What will you do to be part of the challenge?” Dr Firth asked.

Dr Anne Child provided an update on the effects of Irbesartan on aortic dilatation in Marfan syndrome study (AIMS) (UKCRN 9818). Irbesartan is being trialled as an adjunctive therapy and patients enrolled in this trial will not be expected to stop taking current medication. It is a nationwide study, recruiting over a 24 month period, and at the time of the
remain, however, a number of challenges and an accelerated review process. There fee reductions for regulatory submissions for drugs for these orphan conditions include the European Medicines Agency (EMA) for explained. Incentives offered by the to orphan drug regulations, Dr Eagleton others) getting involved? Partially thanks to returning on investment for pharmaceutical companies. So, why are BioMarin (and return on investment for pharmaceutical companies. But small patient populations mean low results from defects in lysosomal function. Diseases, a group of approximately 50 rare inherited metabolic disorders that are thought to have Marfan syndrome and yet only 9,000 cases have been diagnosed in the UK; this figure should be in the region of 18,000. The study needs 500 participants and the clock is ticking. Dr Child called for the audience’s help in meeting this number.

Dr Terence Eagleton warned that the audience may consider him to be ‘an exotic beast’ – he works in industry, for the biotech company BioMarin. Dr Eagleton reminded attendees of the numbers - there are around 8000 rare diseases and the number is growing year on year. In Europe there are 30 million patients with rare diseases. His particular area of interest is Lysosomal Storage Diseases, a group of approximately 50 rare inherited metabolic disorders that result from defects in lysosomal function. But small patient populations mean low return on investment for pharmaceutical companies. So, why are BioMarin (and others) getting involved? Partially thanks to orphan drug regulations, Dr Eagleton explained. Incentives offered by the European Medicines Agency (EMA) for companies researching or developing drugs for these orphan conditions include fee reductions for regulatory submissions and an accelerated review process. There remain, however, a number of challenges when working on orphan conditions, not least of them a small but geographically disparate patient population.

But despite such challenges research into orphan conditions has benefitted from enormous growth over recent years. It would seem that the words of people like Alastair Kent of Genetic Alliance UK - who spoke of his desire to see rhetoric changed into reality when it comes to this kind of work – are actually being heeded.

2. Pioneering breast cancer study gets off the ground

A rare cause of genetic susceptibility to breast cancer has been linked to an increase in a tumour marker protein. Researchers hope this will improve diagnosis of the underlying genetic cause of the disease for these high-risk patients, and allow better, more tailored treatments.

Around one percent of breast cancers are thought to be caused by an inherited mutation in the p53 gene, and they are often associated with very young onset disease. Researchers have now identified a link between an underlying p53 mutation and a marker protein called HER2, which is known to be amplified in a number of other cancers. HER2 amplifications are found in 15 – 20 percent of breast cancers, and are currently used to determine whether to treat someone with the targeted drug Herceptin. It is hoped this link will improve genetic diagnosis and allow less toxic treatment for those with the p53 mutation.

Initial research from the COPE (cohort study of p53 early onset breast cancer) project (UKCRN 8028, http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=8028), identified an increase in HER2 levels in 10 of 12 tumour samples taken from carriers of the p53 gene mutation. These results have recently been validated by a similar study of 30 patients in the USA.

The University of Southampton team is now collecting all the samples, or ‘blocks’, of breast tumours from patients in the UK that have been diagnosed with underlying p53 mutations over the past 20 - 30 years. Despite the fact this is likely to number only around 100, chief investigator Professor Diana Eccles explains that this is no mean feat. “Each centre needs to identify relevant cases – which isn’t a trivial piece of work in itself – trawl through the records, get pathology reports, make sure everything is properly anonymised, and then organise the transfer of material here.”

This potential logistical nightmare has been avoided thanks to the National Institute for Health Research (NIHR) Genetics Specialty Group. Through them, the COPE project has had access to the support services provided by the NIHR Comprehensive Clinical Research Network (NIHR CCRN) which consists of 25 Comprehensive Local Research Networks (NIHR CLRNs). “This work is really complicated and difficult. A lot of vital and time consuming administrative leg-work has been provided by CLRN-funded positions across participating genetic services,” Professor Eccles says. “Basically it means it’s possible for us to make contact with one individual who’s designated to help with this study, and that’s been a great help.”

In addition to having CLRN administrators identifying cases and overseeing transfer at centres throughout the country, COPE has benefited from having positions within the University of Southampton. This has allowed them to work with the clinical
teams to establish efficient methods to record material as it comes in.

The project’s aim is not only to confirm the theory that inherited p53 mutations can be identified by preferentially looking at very young breast cancer patients with amplified HER2 levels in their tumour, but also to understand the type and timing of other key molecular events that occur in those cancers. "We think that a p53 mutation drives a particular oncogenic pathway," Professor Eccles explains. "If we can find a common theme - ideally early, critical molecular events - we may have a target to direct new drug treatments. In the future we might even have the potential to prevent these devastating cancers from developing." She also hopes it will reduce the need for chemotherapy, which itself has the potential to cause cancer. Currently, patients have both chemotherapy and Herceptin; it could be a step towards long-term recovery if gene carriers were identified, as treatments could possibly be limited to Herceptin.

The COPE study is now about halfway through recruitment, and the team expect that by the end of the year they will have collated all the tumour samples and have begun primary analysis. "These things always take longer than you think, but I'm not sure if we would have got there without the help from the CLRN to get the current mechanisms in place," Professor Eccles says.

3. Greater Manchester excels in clinical trial recruitment

Recruitment to clinical trials led by the Regional Genetics Service in the Greater Manchester area has increased rapidly thanks to the input of the National Institute for Health Research Genetics Specialty Group. The region’s Clinical Local Research Network (Greater Manchester CLRN) is providing support in terms of resources and access to a dedicated team of research facilitators to speed up the enrolment process and take pressure off the researchers themselves.

This support ranges from studies in their final stages to those that are just starting out. One such study, in its preliminary recruitment period, aims to identify genes that are responsible for rare inherited bladder problems in children.

Dr Bill Newman, NIHR Regional Genetic Lead for the Greater Manchester CLRN explains that this study (UKCRN 10796, http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=10796) began after the discovery of the genetic cause of a rare condition called urofacial syndrome, which is characterised by problems properly emptying the bladder and abnormal facial expressions when smiling. The team wants to identify other genetic factors that can cause this condition, and to see if they are responsible for more common causes of childhood renal failure.

At the other end of the recruitment spectrum, the Greater Manchester centre is also involved in a UK wide and international collaboration looking to better understand the genetics of inflammatory bowel disease (IBD) (UKCRN 7612, http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=7612). Predominantly focussed on recruiting patients with IBD from South Asian backgrounds, as these patients have been underrepresented in genetic studies of IBD to date, the region was initially "behind the curve" in terms of recruitment, says Dr Newman. "Since the NIHR Comprehensive Clinical Research Network (CCRN) has come on board we’ve caught up with our recruitment and the numbers have increased enormously." The support from NIHR CCRN has also facilitated the set up of additional centres in Bradford, North Manchester and Birmingham. The UK IBD Genetics Consortium has now recruited 1500 patients, a third of the worldwide total contributing to major gene mapping projects.

PROCAS (Predicting Risk Of Cancer At Screening) (UKCRN 8080, http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=8080) is the major success story of NIHR portfolio study recruitment in the North West. It is funded by an NIHR Programme Grant for Applied Research which aims to more accurately predict the breast cancer risk for women who attend routine NHS breast screening. Led by Professor Gareth Evans at the University of Manchester, it has recruited over 49,000 women to date. "PROCAS has been very successful, and that's certainly been facilitated and supported by the NIHR CLRN dedicated nurse," says Dr Newman. Manchester also contributes significantly to the Deciphering Developmental Disorders (UKCRN 9955) project, studying the genomic basis of severe developmental disorders to improve diagnosis and management.

“Since the NIHR Comprehensive Clinical Research Network (CCRN) has come on board we’ve caught up with our recruitment and the number have increased enormously.”
4. Support staff crucial to successful clinical genetic studies

Increasing recruitment into clinical studies is a key objective of the NHS and its research arm, the National Institute for Health Research (NIHR). However, such recruitment is time-consuming and labour-intensive, so specific funding and trained staff are required. Twenty-five Comprehensive Local Research Networks (CLRN) provide funding for research nurses, administrators and co-ordinators to help cut through the red tape of research and development (R&D) approval, and consent patients into studies.

"Not only are they key to the recruitment into research studies, having someone in place to do the R&D paperwork is brilliant. It wouldn't happen without them," notes Gill Borthwick, National Research Coordinator for the NIHR Genetics Specialty Group (GSG), who was speaking at a recent conference, the GenRes study day, for genetic research nurses, counsellors and co-ordinators. This study day offered participants the chance to meet people from other centres, share ideas and discuss any problems.

"For instance, while no one feels undervalued, some question whether everyone appreciates the full extent of their work. Not only does each research nurse or administrator have a large number of trials to support, they have a range of responsibilities that extends far beyond recruitment. Julie Phipps, a genetics research nurse in Clinical Genetics Oxford, was initially appointed to assist on a few genetic studies. She now works with over 12 studies. "It was a mountain of paperwork at first and even now there doesn’t seem to be enough hours in the day," she says. "At the moment I do everything from gaining NHS Trust approval and raising the profile of the department, to recruitment and setting up study sites in other centres."

Similarly, Isabel Giblin, based at Great Ormond Street Hospital, London, is both a co-ordinator for the Central East London GSG and a research administrator for a clinical trial investigating non-invasive prenatal diagnosis, called RAPID. For that she is responsible for setting up new recruitment sites for the trial in the UK.

"If you’re a lead site, you are responsible for setting up recruitment centres in other areas in the UK," explains Lucy Harrison, a research nurse at the Wessex Clinical Genetics Service. "You have to send the other centre a file with all the ethical agreements, the funding information and any other paperwork that needs localising. Then during the study recruitment, you have to assist and support the other centres."

But, as Gill notes, each NIHR Portfolio study needs to recruit their target number of participants before the funding ends – those that haven’t will be considered a failed study by the NIHR. As such, another support staff role is to monitor recruitment, and be ready to apply for an extension on the funding if necessary. "It’s all activity-based funding, so I’m constantly thinking about research from a financial point of view," says Isobel. "If we have the R&D approval then we need to recruit people into the study. You have to think about how to promote it, and get the support of clinical geneticists."

Julie has succeeded in increasing recruitment through mentoring other centres, having regular meetings with them, and involving the consultants in the process. "Consultants enjoy discussing their research, so by getting them to speak to geneticists in different centres you get an influx of potential candidates" she explains.

"This approach raises awareness of research projects with clinicians who then ask if certain patients are suitable – it’s really effective."

"The role is very much one that you can develop and make your own," says Lucy. There are opportunities to bring in your own ideas, or request funding for training courses. However, an aspect that is thought to put some nurses off is the fact contracts are on a rolling, yearly basis. "The funding doesn’t come with a project, it comes from the CLRN each year - we don’t even know if we’ve got a job in 2013" says Julie.

"CLRN funding is based on successful recruitment to studies; we’re really motivated to improve recruitment to our research studies so we can justify our role to the CLRN."

During the GenRes study day, another problem discussed was the excessive amount of paperwork associated with R&D approval, a particular issue for trials involving rare genetic diseases. "We want to have an agreement in place by the end of the year that if you have a study that’s non-interventional, low risk, and no money is changing hands, then if the lead site approves it, it’s automatically approved in all other centres," explains Gill. Hopefully this will ease pressure on individual centres – for example, if a study involves a disease with only five known cases in the country, one centre may spend months gaining R&D approval to recruit only one, crucial, patient.
Improvements to the recruitment process are welcomed by the research nurses, who feel their time is often taken up with paperwork when it could be filled with consenting patients into trials. While such measures will not only benefit staff, they will also benefit the patients and families involved. For them, quick and efficient inclusion in clinical trials could speed up access to treatment and reduces emotional stress.

5. Genetic Counsellors and their role in research

“There has been a great step forward over the last few years. Increasingly, genetic counsellors are becoming chief investigators on studies. Traditionally it's usually been a scientist or medical professional, but things are changing.”

Caroline Benjamin, speaking, is the co-opted Genetic Counsellor member of the NIHR Genetics Specialty Group.

People are often more familiar with the geographical organisation of the Comprehensive Clinical Research network (CCRN), how it is split into 25 Comprehensive Local Research Networks (CLRN)s covering the whole of England by region. But it is also organised so as to provide topic-specific expertise and for this 24 Specialty Groups, covering disciplines from age and ageing to surgery, exist. The NIHR Genetics Specialty Group is one of the 24, lead by Sir John Burn and managed by Gill Borthwick.

As a co-opted member of the Specialty Group, Caroline does not specifically represent the AGNC. Her role is to ensure relevant genetic counselling input on NIHR portfolio studies and act as a point of contact for genetic counsellors who are – or are seeking to be – involved in such research.

On top of this she also works to support and encourage genetic counselling research on the NIHR portfolio. So as well as now participating in genetics clinical research projects generally, genetic counsellors will also act as chief investigators on research in their own specialty.

In this regard Caroline talks about ongoing portfolio studies funded by NIHR Fellowships. These include Rachel Belk’s work (UKCRN 9157) looking at the challenges and advantages of a visual language when discussing genetics in British Sign Language. She also mentions a study led by Gillian Crawford (UKCRN 10917) to explore the consent and disclosure practices surrounding clinically relevant incidental findings from genetic tests and Chris Jacob's research (UKCRN 12611) to help better understand communicating cancer genetics test results.

Caroline says that one important role for the National Genetics Specialty Group is to “scan the horizon for new research that could benefit patient recruitment in a local centre or becoming involved in governance of research in their local centre through to writing grant proposals and applying for funding.”

If any genetic counsellors wish to find out more regarding the work of the NIHR Genetics Specialty Group or research in general they can contact Caroline on caroline.benjamin@lwh.nhs.uk.

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

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

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

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

The Deciphering Developmental Disorders (DDD) project, which is a collaboration between the Wellcome Trust Sanger Institute and all 23 NHS Regional Genetics Services, is now nearing the end of its second year of recruitment. At the date of writing, over 150 clinical geneticists had recruited patients to the DDD study and collectively we had recruited over 3,600 children with severe undiagnosed developmental disorders, and their parents, from all around the UK. The study recently received approval to extend recruitment until April 2015, and to remove the age limit so that adults can now be recruited into the study with both parents. However, we are still below our recruitment target (see Fig. 1) so please consider all undiagnosed individuals and families with severe and extreme phenotypes such as:

- neurodevelopmental disorder
- congenital anomalies
- abnormal growth parameters (height, weight, OFC; 2 items >3sd, 1 item >4sd)
- dysmorphic features
- unusual or extreme behavioural phenotypes
- genetic disorder of significant impact for which the molecular basis is currently unknown

Since the inception of the project, the cost of sequencing has continued to decline and the diagnostic utility of parent-offspring trio exome analysis has been conclusively demonstrated in numerous publications.

Therefore, although we are continuing to perform high resolution (2M probe) array-CGH analysis of the proband, we have reconfigured the project and stopped SNP genotyping of families in order to liberate more funds for exome sequencing. We are expecting to have a full set of exome and array data on our first 1000 trios in the New Year, and have developed custom analysis pipelines to facilitate both clinical reporting of likely pathogenic variants to individual patients via their referring clinician, and scientific research into new variants and genes associated with developmental disorders (DD).

As of September 2012, we started reporting individual results back to clinical teams. Most centres have now received at least one variant from us, either from the array analysis or the first batch of exomes. We have reported around 50 copy number variants via DECIPHER, ranging from ~400bp to 14.5Mb in size, and if no pathogenic variant has yet been identified we are feeding back ‘normal’ reports. We aim to feedback only variants that are likely to contribute to the child’s DD, specifically:

- any variant overlapping a known DD gene with relevant genotype, mechanism of action and phenotype(s); de novo, segregating and homozygous genic deletions>100kb and duplications>250kb; and large genic variants >500kb with unknown inheritance.

We have also reported 24 single nucleotide variants identified using trio exome sequencing including 22 de novo changes in known DD genes, as well as one homozygous and one compound heterozygous loss of function variant in autosomal recessive genes associated with DD. In all cases, we believe these variants are the cause of the child’s DD and, in one case, the disorder is likely to be treatable.

Figure 1: DDD monthly recruitment
Non-invasive prenatal testing and RAPID programme update

Melissa Hill and Lyn Chitty, Clinical and Molecular Genetics, Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust

Helen White, National Genetics Reference Laboratory, Wessex

We are currently developing DECIPHER to display sequence variants (as well as copy number variants) in a new interactive browser, which should be available in early 2013.

In addition to reporting back likely pathogenic variants, particularly in known DD genes, we are also investigating novel candidate genes and undertaking ‘in-the-round’ analyses to delineate the genetic architecture of DD. Although primary research analyses will be carried out at the Sanger Institute, we are keen to encourage researchers across the NHS Regional Genetics Services to lead and participate in complementary research projects. There are numerous projects that can be undertaken on subsets of the DDD data, focusing on a range of topics from specific diseases, phenotypes or biology, to technology, policy or ethics. In order to maximize the research and diagnostic benefits from DDD, foster collaboration and develop research careers, we want to encourage as many people with research interests in the Regional Genetics Services to get involved. Details are available via DECIPHER/ DDD once you’ve logged in, so please get thinking of ways you can contribute.

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

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

RAPID is a five year research programme that aims to improve the quality of NHS prenatal diagnostic services by evaluating early non-invasive prenatal testing (NIPT) based on cell free fetal (cff) DNA in maternal plasma. Since our launch in July 2009 the RAPID programme has made significant progress in accomplishing its aims. A key achievement has been our work with the service laboratories to gain UKGTN approval for fetal sex determination in pregnancies at risk of congenital adrenal hyperplasia and X-linked disorders (excluding haemophilia) and for NIPT to diagnose achondroplasia and thanatophoric dysplasia. Here we provide an update on our progress and describe the current status of NIPT in the UK.

Collection and processing of maternal blood samples

The development of NIPT is reliant on the collection of blood samples from women (and partners) undergoing invasive testing. Sample banks for use in developing NIPT tests have been established at National Genetics Reference Laboratory, Wessex (NGRL) and Great Ormond Street Hospital (GOSH) and we have now collected over 9000 samples. Over 40 units around the UK are helping us with recruitment.

Working with cffDNA is technically challenging and it is important that we maximise the yield and quality. To this end, we have explored issues such as the best time to process samples and what collection tubes to use.1 In addition, the RAPID team at NGRL (Wessex) have developed a real-time PCR protocol for the detection of hypermethylated RASSF1A suitable for use as a universal fetal marker in clinical practice. This allows us to ensure cffDNA is present in the sample being tested and we anticipate that this assay will improve the reliability of NIPT.2

NIPT for single gene disorders

The development of NIPT for single gene disorders is being undertaken by the RAPID team at GOSH and also by a number of the regional genetics laboratories who are collaborating with RAPID and using samples from the RAPID sample bank.

We have made great progress in the development of NIPT for the haemoglobinopathies (sickle cell disorder and beta-thalassaemia). These tests are being developed in conjunction with the University College London Hospitals (UCLH) and Oxford laboratories, who offer traditional prenatal diagnosis for these conditions. A digital PCR assay for sickle cell disorder has been developed at GOSH which showed high accuracy in preliminary studies.4 Further optimisation of this test is ongoing. In addition, we are exploring sequencing-based approaches for sickle cell disorder and we will be comparing the digital PCR and sequencing approaches. We are also developing a sequencing-based assay for NIPT for beta thalassaemia, cystic fibrosis and FGFR3 mutations.

NIPT for aneuploidies

The development of NIPT for Down’s syndrome (trisomy 21) and other common aneuploidies (trisomies 18 and 13) has moved very fast. A variety of new techniques and technologies have been trialled with varying degrees of success. Currently the most promising approaches are based on next generation sequencing (NGS) and several studies have demonstrated detection rates of greater than 99% with false positive rates of 0.3-1%. The small false positive rate means
NIPT for Down’s syndrome cannot be considered fully diagnostic and positive results should be confirmed by invasive testing. NIPT for aneuploidy was first launched through commercial providers in the USA, Hong Kong, China and Germany. It is now also available privately in the UK with samples being sent for testing in the USA.

NGRL (Wessex) and North East Thames Regional Genetics Laboratory (NERGL) (GOSH) are currently evaluating the performance of NGS approaches in our regional laboratories. Custom-designed bio-informatics software packages for data analysis have been designed by Eastern Sequence and Informatics Hub (EASIH) in Cambridge. Our goal is to develop standards for testing that could be utilised by any NHS service laboratory interested in offering NIPT.

**Economic analysis of NIPT for Down’s syndrome**

The cost of NIPT relative to invasive testing will be a key consideration in how it is implemented. The RAPID team have done a preliminary modelling of possible care pathways and economic costs for implementing NIPT for Down’s syndrome in the UK.5 We have calculated the impact of introducing NIPT into the current antenatal care pathway for diagnosing Down’s syndrome, making the assumption that all high risk women identified by screening would undergo NIPT, and that those with a positive NIPT result would have a confirmatory invasive test. We also considered using NIPT as a replacement for current screening programmes. The models show that, with considerations for costs per test and screening cut off, NIPT can compare positively with invasive testing for relative costs, cases detected and numbers of miscarriages, however, fewer non-trisomy 21 chromosomal abnormalities would be detected. A more detailed analysis is ongoing with various care pathways being modelled. The analysis is being developed together with the National Screening Committee.

**Exploring stakeholder views and experiences**

The RAPID team are exploring ethical and psychosocial issues in a number of ways, including ethical analyses6,7 and large questionnaire studies looking at women (N=523) and health professional (N=393) views on factors that impact informed choice8 and women (N=350) and health professional (N=181) preferences for various attributes of diagnostic tests.9 We are also conducting a series of studies using a qualitative approach with focus groups and one-to-one interviews to gather stakeholder views. We have interviewed women who have used NIPT for fetal sex determination [N=44]10,11 or for the diagnosis of a skeletal dysplasia (N=6); couples at risk of single gene disorders (N=30); women having Down’s syndrome screening and testing (N=27); and health professionals (N=79).

Both service users and providers are very positive about the introduction of NIPT. A number of concerns were raised regarding widespread implementation. Participants emphasised the need for any new test to be highly accurate and thoroughly validated. There was concern that people may not give as much thought to having a blood test compared to an invasive test, or that it may be viewed as routine and as such NIPT may negatively impact on informed consent. In addition, there was concern that the simplicity and lack of risk associated with a blood test may lead to increased pressure on women to undergo testing and terminate affected pregnancies. The need for NIPT to be offered through specialist services was emphasised by both service users and providers.

Notably, health professionals felt that the concerns about NIPT could be overcome if structures for appropriate support and counselling were in place. In particular, it will be essential to ensure that NIPT is offered in a way that promotes informed choice so that routinisation of testing is avoided and women are prepared for a result which may require difficult decisions to be made. Ongoing education and training of health professionals will be important, and guidelines and regulation are needed for effective implementation.

**Next steps**

- We are exploring the use of NGS using the MiSeq platform for NIPT for a wider range of single gene disorders and hope to submit further gene dossiers in the near future.
- We are planning an implementation study for NIPT for aneuploidy. We are in discussion with the National Screening Committee so that we address the issues that are vital for widespread implementation of this new technology. Any study will need to go beyond laboratory evaluation and will include development of health professional and patient education, an evaluation of uptake and a detailed health economic assessment.

**How can you help?**

- If your service laboratory would like to develop NIPT for a specific single gene disorder not mentioned here, please contact us. If we have samples in the sample bank we would be keen to help you develop further new tests.

“The cost of NIPT (for Down’s syndrome) relative to invasive testing will be a key consideration in how it is implemented”
ASHG Award for Excellence in Human Genetics Education
Professor Alan Emery

The BSHG congratulates Professor Alan Emery who was awarded the American Society of Human Genetics (ASHG) Award for Excellence in Human Genetics Education on November 10 2012.

Professor Emery (b. 1928) was recognised by the ASHG for his eminent work in education through lecturing and mentoring as well as his extensive writings which include over 400 peer-reviewed articles and 26 books covering all aspects of human and medical genetics. Professor Emery was also the first to describe a form of muscular dystrophy that is now referred to as Emery-Dreifuss Muscular Dystrophy with the Emerin protein named after him.

Among his many accolades, Professor Emery has been elected a fellow or honorary fellow in ten different societies, most notably the Royal Society of Medicine and Green Templeton College, University of Oxford, and has received many awards, including the Lifetime Achievement Award from the World Federation of Neurology and the Cockcroft Medal from the University of Manchester.

Apart from his academic work, he also paints and is a published poet. As stated by the ASHG "For many in the field of human genetics, Professor Emery is simply known as ‘the expert’."

References

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

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Changing Futures
Kate Dack, Public Programmes Manager, Nowgen

A new set of online resources – developed by teenagers for teenagers – exploring cystic fibrosis (CF) and gene therapy were launched recently. The Changing Futures project, led by Nowgen in Manchester, worked with young people with CF, artists, clinicians, educators and scientists, to create an engaging and accessible website for teenagers.

Gene therapy for CF has adopted a high profile in 2012 with clinical trials underway and many patients want to find out more, so this website helps to introduce this important research area to both teenagers affected by CF and pupils learning about genetics in school. People with CF are advised not to meet each other due to the risk of cross-infection, meaning opportunities for patients to discuss research for CF are limited.

Supported by a People Award from the Wellcome Trust, the Changing Futures project held a series of creative workshops to enable young people living with CF to share their experiences of CF and views on gene therapy. With the help of the project team, the teenagers created a number of resources including filming interviews with scientists, a music mash up video and producing classroom resources for teachers to help others better understand cystic fibrosis and gene therapy.

The Changing Futures website comprises three zones: The CF Zone, The Gene Therapy Zone and The Teacher Zone. The first two zones explore how CF is inherited and the effect it has on people’s lives, as well as the history of gene therapy. The third zone is specifically for teachers, and includes educational activities, interviews with a range of experts and links to further information.

www.changing-futures.co.uk
Website Review: Changing Futures

Marco Narajos, Project manager and literary editor of The MedSchool Project, Ashby School, Ashby-de-la-Zouch

Public engagement in science, to me, is fundamental as it plays a huge role in creating the world’s next generation of scientists. But not only that; public engagement allows greater access to topics that can be difficult to understand – that is the mission of Changing Futures.

Providing educational resources, especially for young people, can be especially difficult when the subject matter is diverse and complex. This I know first-hand from blogging about medical topics aimed at students. As a sixth-former hoping to study medicine at university, I sometimes find it hard to find resources that are kept simple enough to understand but detailed enough for me to learn something new.

For example, although there are numerous books on CF and gene therapy, I find there is little or no middle ground between brief explanations for children and medical books that are often too complicated. So while reading books to gain new knowledge is essential, for many complex topics, such as CF and gene therapy, creative resources – animations, interviews, music videos and video diaries – are needed.

This is where Changing Futures comes in. Changing Futures (aptly named with the same initials as cystic fibrosis) is an educational website filled with up-to-date information about CF and gene therapy, pitched at the perfect level.

The cystic fibrosis section of the website includes videos from experts explaining the science behind the condition. There are also interviews, including those with a patient adviser, a CF nurse specialist, and with two of the teenagers with CF who participated in the project. Their video diaries show what teenagers with CF go through in their daily lives - their daily routine, the physiotherapy involved and all the medication they are required to take. There is even a music video inspired by their physiotherapy exercises; although how the music is relevant to CF, I do not know!

Although the videos are very upbeat and uplifting, there is a serious undertone. The girls in the video diaries lead such different lives; and to think that there are around 9,000 people with CF in the UK alone, this is quite astounding. The videos are not only educational, but they also help non-CF viewers to reflect on their own lives. For those with CF, the video diaries may also serve as a reminder that they are not alone.

On gene therapy, the website features an interactive timeline with videos to explain each of the events listed. I found the video on liposomes most interesting as it relates to science when applied ‘in the real world’. There are also videos on gene therapy made from teenagers’ perspectives, which although more emotive than scientific, they do emphasise the issues experienced by people affected by CF.

The Teacher Zone on the Changing Futures website may also provide an invaluable resource for science teachers who wish to inspire young people to pursue science at university. As I run a medical club at school, I could make good use of the practical resources in the Teacher Zone to show others how to make their own mucus or how to extract DNA, for example.

As a student and as a teenager, I would definitely recommend this resource to anyone who wants to know more about CF and how it affects young people. Changing Futures is a great web resource that deserves a lot of kudos for bringing to light one of the UK’s most common genetic conditions and creatively exploring gene therapy.
Genetics and Insurance: A free booklet about what you need to know and what you need to tell

Buddug Cope, Genetic Alliance UK

The final version of the booklet, called Genetics and Insurance: what you need to know, what you need to tell provides a comprehensive overview of issues relating to genetics and insurance. The aim of this booklet is to be a practical source of information for people before and during the time they are obtaining insurance products. Its purpose is to explain what people need to tell an insurance company and also what people do not need to disclose. In fact, we believe it provides helpful information for anyone interested in insurance products.

Topics covered in the booklet include explanations and descriptions on:

- what is a family medical history
- genetic tests and why insurance companies need to know about diagnostic tests, but not predictive tests
- what to do if you are receiving treatment or therapy for your condition
- what is the moratorium & concordat – the voluntary agreement between the UK Government and the British Insurance Industry
- what happens if the insurance company needs additional information from your GP or your hospital doctor

This booklet also provides information on how to find an appropriate insurance policy from different insurance companies, and to ‘shop around’. After all, not all insurers are the same. We also provide tips on how to find an independent financial advisor or insurance broker who will help to find the best possible quote.

Our aim is to make sure that this booklet is practical and is used by anyone wanting more information about genetics and insurance. The booklet will be kept up to date, so if the concordat and moratorium change in the future, this booklet will continue to provide accurate and useful information.

We are grateful to everyone who contributed their time and effort to help us produce this booklet.

The booklet is available to download and print out for free from [www.geneticaalliance.org.uk/insurance.htm](http://www.geneticaalliance.org.uk/insurance.htm). If you do not have access to the internet, or if you would like a paper copy of the booklet posted out to you, please contact us at the Genetic Alliance UK office on 020 7704 3141.
NGRL Manchester continues to provide four core services (DMuDB, SNPCheck, bioinformatic resource analysis and bioinformatic training), supported by related grant funding and consultancy. Project grant funding is being sought to support continued service provision over the coming years.

The team has said farewell to Simon Williams, Clinical Bioinformatician, and Jasmin Opitz, Health Informatics Scientist. Both have made exceptionally valuable contributions to NGRL’s outputs over the last 18 months and we are sorry to see them go. New team members are due to be recruited very soon – find out more in our next update!

**DMuDB**

DMuDB now has 57 subscribing laboratories from 22 different countries and significant amounts of data have been received from many of them. To keep up to date with new data, users can check the DMuDB home page for weekly reports, subscribe to DMuDB data alerts (email support@dmudb.net with ‘subscribe DMuDB data alert’ in subject line), and visit www.ngrl.org.uk/Manchester/page/dmudb to see a summary of data in DMuDB. UK laboratories should note that if they do not have a subscription to DMuDB then they continue to have free access to all data submitted by other UK laboratories, but will not be able to see data submitted by subscribing non-UK laboratories. Non-UK data in DMuDB includes:

- **BRCA1** - 230 variants
- **BRCA2** - 220 variants
- **CDH1** - 7 variants
- **CDH6** - 27 variants
- **EXT1** - 104 variants
- **HFE** - 972 variants
- **MLH1** - 20 variants
- **MSH2** - 38 variants
- **MSH6** - 38 variants
- **MYBPC3** - 55 variants
- **MYH7** - 160 variants
- **SDHB** - 3 variants
- **TP53** - 12 variants
- **BRCA1** - 200 variants
- **CDH1** - 7 variants
- **MLH1** - 20 variants
- **MSH6** - 27 variants
- **TP53** - 12 variants
- **BRCA2** - 220 variants
- **CDH1** - 7 variants
- **MLH1** - 20 variants
- **MSH6** - 27 variants
- **TP53** - 12 variants

To find out more about subscription see the DMuDB login page https://secure.dmudb.net/ngrl-rep/Home.do or contact us at support@dmudb.net.

The next planned development for DMuDB will focus on automating extraction and loading of data from laboratory systems. This follows the successful trial of the application to extract data from a lab spreadsheet and load it into an LOVD database. Anyone interested in trialling this automated system should get in touch (support@dmudb.net) as we are working with individuals to implement it where it can be of benefit.

NGRL continues its involvement with the Human Variome Project and has been seeking feedback from the UK genetics laboratories.

**SNPCheck**

SNPCheck now includes the option to check primers against the 1000 Genomes Project dataset independently of dbSNP, and also the Exome Sequencing Project dataset. For 1000 Genomes data this provides users with a breakdown of Minor Allele Frequencies by population group, more readily available in SNPCheck. Since the release of the 1000 Genomes data we have received regular requests for help to find details of specific SNPs. In response to this we have developed a simple online query tool, which enables users to find a SNP quickly, and all the population frequency information associated with it. The query tool can be accessed at: http://ngrl.manchester.ac.uk/1kg_querytool/

As described above, we have reformatted the 1000 Genomes Project dataset to make key information, such as Minor Allele Frequency (MAF) scores by population group, more readily available in SNPCheck. NGRL will be launching a new online resource which brings together all of our work on bioinformatic tool reviews, data provision and recommendations for effective use of these resources – look out for announcements on the main NGRL website!

**Bioinformatic tool analysis**

We have carried out a review and analysis of bioinformatic tools for the prediction of missense variant pathogenicity. A report has been produced providing results and recommendations – this can be downloaded from the NGRL website. An overview of the tools assessed is also provided on the NGRL website – information supplied covers an explanation of how the tools work, and their strengths and limitations.

NGRL will be running a new free online course on bioinformatic tools for the prediction of missense variant pathogenicity. The course is planned for 15-17 May 2013.

**Training**

NGRL and Nowgen bid farewell to Bioinformatics Training Officer, Tom Hancock, late in 2012 and are in the process of recruiting a new team member to take on the task of delivering the popular bioinformatics training courses run for scientists and clinicians. The next Bioinformatics for Genetic Scientists course is planned for 15-17 May 2013.
A study day showcasing Sheffield Diagnostic Genetics Service

Ed Atack, Clinical Scientist, Sheffield Diagnostic Genetics Service

Grant funded projects

**GEN2PHEN** – this project has received a 6 month extension to enable further work to be done beyond the original planned deliverables. Work is focused on two main themes – federation and sharing of variant data, and the collection of phenotype data. The project will end in June 2013.

**EuroGentest** – as part of this project NGRL is organising a workshop entitled *The challenges of getting clinical data into databases*. The workshop will look at the collection of clinical-quality data, including the need for phenotype data collection. Its aim is to bring together experts to develop guidelines for data collections, system implementation, standardisation and quality control. The workshop is planned for the end of January 2013.

**Consultancy** – NGRL Manchester is available on a consultancy basis to offer support and expertise in bio- and health informatics. Anyone requiring this service should contact Andrew Devereau (andrew.devereau@cmft.nhs.uk) or Kathryn Robertson (kathryn.robertson@cmft.nhs.uk).

Andrew Devereau
andrew.devereau@cmft.nhs.uk

Sheffield Diagnostic Genetics Service (SDGS), located at Sheffield Children’s NHS Foundation Trust, hosted its first annual Study Day on 14 September 2012. Local A-level students, undergraduates, postgraduates and NHS scientists from other pathology disciplines were treated to talks, tours and observation sessions, giving them an insight into the workings of the Sheffield laboratory, a fully integrated, mixed discipline service that consists of technical and scientific teams with both molecular and cytogenetic experience. Echoing the principles of Modernising Scientific Careers, the study day was designed to illustrate and capture the links between pathology disciplines in an action packed, ‘hands-on’ day.

The schedule was split into two main themes - technique and service. *Technique* provided two presentations on the theory of cytogenetic and molecular genetics followed by a tour of the department. This was followed by four mini-observations showcasing karyotyping, FISH, genotyping and sequence analysis giving participants first hand experience of laboratory processes and some aspects of genetic analysis. The afternoon *Service* sessions highlighted the constitutional and oncology services that SDGS offers as well as their links with clinicians. Rounding the day off was an open-question session for all technical and scientific staff.

Feedback from attendees was wonderfully positive, describing the day as well organised and comprising a good balance of theory, observations and discussion. One A-level student from Sheffield was delighted by the valuable experience he will be able to utilise for university applications, while another attendee was intrigued to see how cytogenetic and molecular labs now work as a dual discipline.

Though the first study day of its kind at SDGS, plans are already being made for the event to run annually.

For more information, contact edward.atack@sch.nhs.uk
www.sheffieldchildrens.nhs.uk/SDGS.htm
Clinical genetics is undergoing a period of rapid change as we try to adapt to new technological advances and integrate these into patient care. While much of this focus revolves around the diagnostic power of new sequencing platforms and the subsequent difficulties of personalised genomic data interpretation, another, perhaps less well highlighted but equally important change is the imminent advent of clinically available gene therapy. On 2 November 2012 it was announced that the European Commission had approved the first commercially available gene therapy, Glybera, for the treatment of lipoprotein lipase deficiency. While this particular therapy is for an extremely rare disease, the announcement marks a key milestone in the development of gene therapy technology with a number of other gene therapies rapidly approaching the point of eligibility for clinical approval. These are exciting times for the field and a flavour of this was captured at the recent 20th Annual Congress of the European Society of Gene and Cell Therapy held in Versailles, France.

A major strategy employed by many of the gene therapies currently in clinical trial is the genetic modification (via viral vector) of haematopoietic stem cells (HSCs) that have previously been collected from patients. By molecularly correcting the genetic defect in these cells in vitro and then reinfusing them by way of autologous HSC transplant, the patient’s immune system can be reconstituted with his or her own cells that now express the gene of interest. This strategy has previously been used to treat primary immune deficiencies such as SCID-X1. Unfortunately, when original trials of such therapy were carried out on 20 patients in 1999, five developed leukemia (T cell ALL) owing to proto-oncogene activation following gene insertion. However, follow-up of this same cohort of patients 13 years later shows overall survival at 90%, which is at least comparable to the only available alternative of allogeneic HSC transplant. In light of this, further trials with similar methodologies are now underway for ADA-SCID, where some 29 patients have been treated to date, Wiskott-Aldrich syndrome and chronic granulomatous disease.

Ex vivo genetically modified HSCs are also being clinically trialled in the treatment of leukodystrophies, including metachromatic leukodystrophy, X-linked adrenoleukodystrophy and globoid cell leukodystrophy (Krabbe disease). This takes advantage of the fact that the myeloid precursors of microglial cells are able to cross the blood-brain barrier from the circulation following HSC transplant, thus repopulating the CNS with enzyme- or transporter-corrected cells that can halt disease progression. One further remarkable use of modified HSCs is in the treatment of HIV infection. In 2007 the now famous ‘Berlin patient’, a man with HIV who developed AML, was given a bone marrow transplant from a donor homozygous for a mutation (CCR5 □32) in the CCR5 receptor used by HIV to gain access to T cells. Five years on he remains essentially free from HIV with good CD4 counts and does not require highly active antiretroviral therapy. In the past year a number of HIV patients have undergone autologous HSC transplants with genetically induced CCR5 modifications to their cells. Their CD4 counts have so far shown promising improvements.

Cystic fibrosis gene therapy has been in the pipeline for many years and it looks as though this vast and long-term project, based in the UK, may be nearing fruition. A phase II randomised, double-blind, placebo-controlled, multidose trial of nebulised liposome CFTR gene replacement therapy is now underway. Patients will be given repeated monthly administrations over a one year period to assess long-term effects on lung function. Previous studies have shown that liposomal delivery of CFTR to respiratory epithelium can significantly improve CFTR channel function and so it is hoped that a beneficial result will be seen. Another disease in a similarly advanced state of therapeutic trials is Duchenne muscular dystrophy, for which oligonucleotide-induced exon-skipping gene therapy is in phase II clinical trials for patients with mutations amenable to exon 51 skipping. This technology uses chemically modified antisense oligonucleotides to repair the reading frame of mutated dystrophin mRNA by inducing the splicing machinery to skip out a specifically targeted and essentially redundant internal dystrophin exon. A similar type of antisense therapy has been developed to treat spinal muscular atrophy and clinical trials of this are now planned, this time delivering an antisense-expressing DNA construct to the CNS using a viral vector.

This short summary must by necessity leave out many of the other topics covered at this meeting including gene therapy of retinal dystrophies, viral-targeted liver gene therapy for haemophilia, anti-tumour engineered T cells and more. In conclusion, a number of bottlenecks remain to the widespread use of gene therapy. These include stable effective gene expression, the immune response to viral vectors and/or transgenes and the risks of genomic integration. However, new technological strategies to deal with these issues are becoming available. Another possible hurdle is the development of an appropriate regulatory framework for gene therapy development, although the advent of approval for drugs like Glybera may start to address this. What is clear, however, is that gene therapy’s clinical arrival is imminent. As a specialty, I believe it is a discipline we must not only be aware of, but also ideally be one in which we seek to be actively involved.

Reference
The Second Cardiff International Genomics Conference, 13-14 September 2012

Professor Dhavendra Kumar, Consultant in clinical genetics, All Wales Medical Genetics Service

In 2009, the Wales genetic and genomic community set out on an ambitious task to bring together leading world class experts in genetics and genomics to Cardiff for a conference to discuss and reflect on the key developments in genomics and the implications for clinical medicine. The first highly successful conference was hosted by the Wales Gene Park and was welcomed with much enthusiasm. This conference led to further collaborations and networking between the Welsh genetics and genomics community and the rest of the world. Three years later the Wales Gene Park was encouraged to hold the second genomics conference.

The organizing group, led by Professor Dhavendra Kumar met on few occasions and agreed Genomics for healthcare and socio-economic progress as the theme for the 2012 genomics conference. The international scientific committee, led by Professor Ruth Chadwick, worked hard to ensure a balanced and relevant set of topics in the final programme. The faculty included some of the leading experts representing major fields of genomics and allied disciplines including Professor Sir John Burn (Newcastle upon Tyne), Professor Hilger Ropers (Berlin), Professor Steve Yearley (Edinburgh), Professor Tony Brookes (Leicester), Professor Sir David Weatherall (Oxford), Professor Michael Katz (March of Dimes, New York), Professor Tim Frayling (Exeter), Dr Hilary Burton (Cambridge) and Professor Peter Farndon (Birmingham).

The conference provided a forum for high level discussion on the current technical state of genomics and future developments of genomic applications in medicine and health. In addition, the panel of international experts highlighted the socio-economic impact of potential applications of genome sciences and technologies in pharmaceutical, agriculture and bio-energy industries. The panel reviewed in detail the ethical, legal and social issues relating to genomics. An emphasis on specific issues relating to emerging economies of the developing world was evident from key presentations. Other highlights of the conference included genomic applications in public and population health, genomic education and training and public awareness and engagement for health and social genomics.

The socio-political highlights of the conference were a brief address by Ms. Lesley Griffiths AM, the Minister for Health and Social Care in Wales and the welcome dinner speech by the Rt. Hon. Mr Carwyn Jones AM, The First Minister for Wales at the conference dinner held in the medieval banquet hall of the 17th Century Cardiff Castle.

Several people contributed to the successful outcome of the conference, particularly Professor Ruth Chadwick (Director, Cesagen, Cardiff University) and members of the organising committee, notably Professor Maggie Kirk (University of Glamorgan), Professor Adam Hedgecoe (Cesagen, Cardiff University) and Professor Denis Murphy (University of Glamorgan). Holding this conference would have been impossible without the full support of the Wales Gene Park and their director Professor Julian Sampson. Special thanks must also be extended to Mrs Angela Burgess and Ms Nina Lazarou from the Wales Gene Park for their tireless contribution ensuring a successful and enjoyable conference. The organisers hope to hold the third conference in 2015.

Professor Dhavendra Kumar with Rt. Hon. Mr Carwyn Jones AM, The First Minister of Wales.

Professor Peter Farndon (Director, National Centre for Genetic Education & Training) with Professor Michael Katz (Director, March of Dimes Birth Defects Foundation, New York)
Association for Inherited Cardiac Conditions second annual meeting – 19 November 2012

Liz Ormondroyd, Cardiac Genetic Counsellor, Department of Cardiovascular Medicine, University of Oxford

The Association for Inherited Cardiac Conditions (AICC) held its 2nd Annual Meeting in London on 19 November 2012. The AICC is the UK national professional body of experts for inherited cardiac conditions (ICCs) - membership includes cardiologists, geneticists, nurses, genetic counsellors, scientists and organisations involved in family support. The day started with the AGM chaired by the President, Professor Bill McKenna. The main question addressed during the AGM concerned the referral guidelines for each of the patient pathways for probands and relatives with inherited arrhythmia, cardiomyopathy and sudden adult death syndrome (SADS). Final versions of these referral guidelines will be available soon on the new AICC website: www.aicc-uk.co.uk.

The first session of the meeting focused on the training needs for the different professional groups as ICC centres emerge and develop.Speakers representing the four professional groups involved in the day-to-day care of ICC patients including cardiologists (Nigel Wheeldon), nurses (Maggie Kirk), geneticists (Dhavendra Kumar) and genetic counsellors (Liz Ormondroyd) outlined current and future training needs. It was clear that there is overlap between the clinical roles of the different professional groups. How much specific genetics and/or cardiology training each require in the context of a multidisciplinary team was discussed with the membership; it was agreed that the AICC has an important role in brokering training for all groups and that this should be a priority for the association.

The next session included very interesting talks on bicuspid aortic valve (Nada Abdulkareem), Ehler Danlos syndrome (Glenda Sobey) and inherited aortic aneurysm and dissection including the large AIMS trial investigating the efficacy of angiotensin II receptor antagonists (Anne Child). Some of the ethical issues in ICCs were presented by Anneke Lucassen, who talked about consent and confidentiality, the limitations and complications of genetic testing and raised the topical subject of 'incidental findings' in genomic studies. Patrick Gallagher gave the pathologist’s perspective on ICC, and pointed out that the median age for sudden adult death (SAD) is 42. However a large minority of victims have no prior cardiac history making a diagnosis post mortem complex; retention of tissue for molecular autopsy can be invaluable. Elijah Behr spoke about the evaluation of relatives after a SAD including the role of exercise ECG; risk stratification in relatives remains difficult especially in Brugada syndrome. Jan Till talked about the diagnosis, genetics and management issues of catecholaminergic polymorphic ventricular tachycardia (CPVT), a rare and highly penetrant arrhythmia condition. This talk highlighted the difficulties of implantable cardioverter defibrillator (ICD) use in CPVT.

There were two sessions involving challenging case presentations from the membership. After prompting from Professor Nigel Wheeldon the week before, this session proved popular with no shortage of presentations. They included cases of less common conditions, such as Danon’s disease and FHL1 cardiomyopathy, the often-encountered difficulties of distinguishing pathogenic mutations from non-functional polymorphisms and consequences for family management, and the implications of making a diagnosis of an ICC for other family members.

There was a talk on ICC service commissioning in the new NHS by Simon Griffith which outlined the new commissioning structures being established. ICC services have achieved recognition for specialist commissioning, and there are plans to tackle geographical variations in priorities, resources and policies. From 2013 specialised services, accounting for 10% of the NHS budget, will become the responsibility of the NHS Commissioning Board but it seems this is still very much under development.

The State of the Art lecture was given by Professor Hugh Watkins, who outlined the current understanding of the genetics of ICCs, focussing on hypertrophic cardiomyopathy (HCM). Since the discovery of sarcomere gene involvement in HCM, the presence of phenocopy genes, multiple mutations, variants of unknown significance and the large minority of patients with no so far-identified genetic cause all complicate the picture. Next generation sequencing is now routine, and there is a potential role for genome/exome sequencing in understanding the genetics of HCM.

The meeting was organised very successfully by Angela Burgess and Nina Lazarou at the Wales Gene Park. Many thanks are due to them, as well as to the organisers and sponsors of the event.
Noticeboard

All members are requested to ensure that the BSHG Office has your correct contact details including email addresses. It is essential to inform us of any changes as soon as possible.

Welcome to New Members

36 new members were elected to the British Society for Human Genetics in June and September 2012

Miss Flora Mary Boyd AGNC
Miss Gemma Devlin AGNC
Mrs Claire L Foo AGNC
Miss Claire O’Flaherty AGNC
Mrs Barbara Mensah AGNC
Dr Anna Christine Michell AGNC
Mrs Julie Marie Phipps AGNC
Mrs Vanita Jivanji AGNC/CGG
Miss Katy E S Barwick BSHG
Mr Simon Boardman BSHG
Dr Simon Bodek BSHG
Miss Laura Cinninon BSHG
Dr Gareth Gerrard BSHG
Mrs Celine M Gervin BSHG
Mr Gabor Martell BSHG
Miss Daisy Mae Moore BSHG
Dr Suran Nethisinghe BSHG
Ms Angelie Ngaha BSHG
Dr Pia Ostergaard BSHG
Mr Harsh Jayesh Sheth CGG
Ms Lianna Jane Sliwczynski CGG
Dr Joelle Tchinda CGG
Miss Nicola Whiffin CGG
Dr Rhoda Aklapass CGS
Dr Claire Bailey CGS
Dr Lucy Bownass CGS
Dr Elaine Fletcher CGS
Dr Stephanie Greville-Heygate CGS
Dr Helen Grote CGS
Dr Sheril Gulgulia CGS
Dr Elizabeth Harris CGS
Dr Mira Kharbanda CGS
Dr Henrietta Lucy Lefroy CGS
Mr Alan Ma CGS
Dr Rachel Hart CGS/SGPH
Miss Claire Holt McKeever Lab Trainees

Direct Debit Subscriptions for 2013/2014

The membership subscriptions will be collected by direct debit during 5-7 April 2013 (see table below for breakdown for each constituent group)

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For UK Members: Preferred option for payment is by Direct Debit but this is only available for bank accounts within the UK.

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

For those members who do not pay by direct debit the Society will be contacting you shortly. Membership Subscriptions are due on 1st April 2013, all payments to be received by the end of April 2013.

Affiliate Membership of the European Society of Human Genetics

For those members who have also opted to take out affiliate membership of the ESHG an additional fee of £44 will also be collected – please note that this rate has not changed as per 2012/2013 through negotiations.

Your ESHG membership will be renewed if subscribed through BSHG unless we are notified by yourselves otherwise before the end of March 2013.
Travel awards

How to apply for Travel Awards

The Travel Award is for current members who have been a member of the Society for at least one year, for travel to overseas conferences, meetings, etc. There are no travel awards available to attend UK based conferences.

It is highly unlikely that retrospective awards will be given.

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

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

Applications should state the benefit of the award to the applicant, and should clearly explain the part the applicant played in the work. A further award will not be made to a successful applicant within three years.

A small review committee has been formed to review applications for these awards. There are four deadlines per year for applications:

1 January 1 April
1 July 1 October

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

Conference reports

1. Keystone Symposia conference report
Liam Hurst

Pulmonary Hypertension (PH), a disease of extensive vascular remodelling, has been well studied, yet the molecular causes are still very much under investigation. Since the discovery of mutations in the gene which encodes a key signalling receptor, Bone Morphogenetic Receptor Type II (BMPR2), in 2000, a plethora of studies have emerged attempting to shed light on the genetic and molecular mechanisms that may contribute to this disease. The first Pulmonary Vascular Disease and Right Ventricular Hypertrophy: Current Concepts and Future Therapies conference, organised by the Keystone Symposia, was held on 10-15 September 2012 in Monterey, California, USA. The conference was organised by Professors Georg Hansmann, Stephen Archer and Margaret Maclean and sponsored by the Bayer Foundation, USA.

My poster presentation was met with great interest. My work focusses on inflammation in PH and how in patients which harbour a mutation in BMPR2, a particular inflammatory cytokine known as tumour necrosis factor alpha (TNF), seen to be raised in patient serum, can further reduce the mRNA as well as protein expression of the receptor, which consequently contributes to a hyper-proliferative response in pulmonary artery smooth muscle cells which may contribute to our understanding of the vessel remodelling commonly witnessed in this disease. Several investigators from around the world were both impressed and intrigued by my novel findings which begs further investigation into understanding the molecular relationship between BMP signalling and inflammation in the disease aetiology.

2. ESHG 2012
Anthony O’Rourke

This meeting was held in the historic German city of Nuremburg. After a faultless travelling experience from Oxford to Nuremburg, I was very much surprised to find the ultra efficient German public transport system was kaput, well at least one ticket machine was, resulting in a lengthy queue at the other. Normal impeccable service was resumed when I encountered the modern and spacious building this year’s conference was being held in. However, it was not long before I had my second surprise of the day. Not one minute into the opening address the Chairman of the ESHG, Herr Professor Schmidtke, had mentioned, and apologised for, The War. Basil Fawlty would have been beside himself. However, given the gravity of events that had occurred in that city it was a necessary moment of reflection.

It was very interesting to see how technology has invaded the audience. There were iPads everywhere and most were gainfully employed. The conference organisers had developed an “app” that allowed delegates to attach notes to presentation abstracts. Although somewhat irritating when individuals stood up to photograph slides, the process of trying to interpret my handwriting and relate the notes back to the 400 plus page abstract book has convinced me that next time I will be eager to utilise the available technology.
The standard of presentations was very high. I was particularly delighted to see so many presentations on skeletal dysplasias, as this is the area in which I currently work, and they helped my understanding of cell differentiation, migration and skeletal morphogenesis. Of course skeletal dysplasias were not the only topic of presentation. The plethora of GWAS talks of recent years were somewhat curtailed with a number of presentations highlighting the power of using exome sequencing to look for de novo mutations in family trios in common, complex disorders. Workshops and satellite meetings were also of interest with a number of them dealing with the quality and utility of recent developments in diagnostic genetics, for example next generation sequencing and non-invasive prenatal diagnosis.

Overall I feel lucky to have been given the opportunity to attend this meeting, and I am grateful to the BSHG for their travel award to allow me to present my poster Frequency of POLR1D, POLR1C and TCOF1 Mutations in a Large Cohort of Patients with Treacher Collins Syndrome.

3. Annual meeting of the International Society of Paediatric and Adolescent Diabetes: October 2012
Victoria McKay

After being awarded a travel grant from BSHG I was lucky enough to travel to Istanbul, Turkey in October to present a poster at the 38th annual meeting of the International Society of Paediatric and Adolescent Diabetes (ISPAD). I had been invited to present my poster entitled A Novel Heterozygous INS Missense Mutation in an Infant with Permanent Neonatal Diabetes Mellitus Presenting with Diabetic Ketoacidosis in the genetics of diabetes section of the conference. This missense mutation causes a leucine for proline substitution in the A chain of the preproinsulin molecule and causes aberrant folding of the mutant protein.

The theme of the conference was global challenges for integrated paediatric diabetes and it was extremely well attended by a global audience with delegates from the USA, Australia, South Africa and Japan in attendance. My poster was very well received and encouraged many interesting and challenging questions. During the conference there were scheduled formal ‘poster tours,’ during which we were asked to formally present our posters to members of the ISPAD scientific committee. My poster tour was led by Dr Rüveyde Bundak who was part of the local organising committee and included presentations on various aspects of the genetics of diabetes including interesting posters on a novel mutation in EIF2AK3 in an Egyptian neonate with Wolcott-Rallison syndrome and an adult patient with Majewski osteodysplastic primordial dwarfism who developed insulin resistant diabetes.

There were some extremely interesting short oral presentations including a Spanish-led collaborative group who sequenced NEUROG3 in patients with severe congenital diarrhoea and either diabetes or enteric anendocrinosis and found biallelic mutations inherited from unaffected parents in all probands. Interestingly these patients had an extremely variable diabetic phenotype but had never become severely hyperglycaemic or ketotic, suggesting the presence of some insulin-producing cells and therefore the hypothesis that NEUROG3 deficiency does not cause complete insulin deficiency. These patients also displayed short stature and/or delayed puberty and had hypogonadotrophic hypogonadism on further testing and more research is ongoing into the hypothalamic expression of NEUROG3. Other sessions included a discussion of the heterogeneous phenotype of patients with HNF1B mutations in renal cysts and diabetes (RCAD) syndrome and a symposium from Professor Fumi Urano on his work into endoplasmic reticulum (ER) homeostasis and work on WFS1 in Wolfram syndrome. His research has found that mutant WFS1 allows upregulation of stress mechanisms within the ER and is looking for ways to maintain the oxidation status of the ER and eventually to find a cure for Wolfram. Work using pioglitazone in animal models has reversed the diabetic phenotype and the results look promising and very exciting for the future.

Professor Andrew Hattersley of University of Exeter presented a wonderful overview of the ISPAD monogenic diabetes cohort from 2001 to present day and the advances in management and treatment this has allowed. Professor Hattersley’s talk focussed on how scientific advances had occurred through managing and investigating patients. He discussed a neonate born with pancreatic and gall bladder agenesis, complex congenital heart disease and diabetes and how the investigation of this patient led to the discovery of GATA6 and its role in pancreatic β cell development. During the symposium a fantastic video of a patient with DEND syndrome was shown; initially this young man was severely developmentally delayed and at the age of two years was still crawling. Investigation of his diabetes found a Kir6.2 mutation responsive to sulphonylureas and within one week of commencing treatment he began to catch up with his development. This result has now been replicated many times and now patients with DEND are given a molecular genetic diagnosis for their diabetes so early that sulphonylureas can be started before any developmental delay is evident.
Forthcoming conferences

Professor Timothy Barrett presented an overview of his pan-European project establishing a database of patients with rare diabetes syndromes. Euro-WABB (www.euro-wabb.org) is focussed on Wolfram, Alström and Bardet-Biedl syndromes and is aiming to collect data on 300 patients over the duration of the project, with the aim being to collect anonymous clinical and mutation datasets and produce guidelines for health professionals managing patients with these conditions. The first of these guidelines, for Wolfram syndrome, is due for completion soon. The long-term goals of the project are to look for new indications for existing drugs and potentially develop interventions and hopefully cure for patients with these conditions. Although focussed on three main syndromes, Professor Barrett is also collecting data on other rare diabetes syndromes including Wolcott-Rallison, Rabson-Mendenhall and others and is very kindly offering free molecular genetic testing and will report back with results!

I did also get a few spare hours to see the vibrant city of Istanbul and visit the Blue Mosque, Ayasofia and haggle for goods in the Grand Bazaar! Overall this was a thoroughly enjoyable and educational conference and I gained an invaluable overview of monogenic diabetes and recent scientific advances in the field of diabetes genetics.

New revolution in genetics & genomics: 27-29 January 2013
Venue: Indian Agricultural Institute, Pusa, New Delhi, India
Contact: dr_icverma@yahoo.com

Biomarkers in Research and Clinical Practice: 13 February 2013
Venue: The Nowgen Centre, 29 Grafton Street, Manchester, M13 9WU
Cost: Public sector: £225, private sector: £350
Contact: Online booking: www.nowgen.org.uk/professional-training-events; bookings@nowgen.org.uk, +44 (0)161 276 5956; Further information training@nowgen.org.uk
Website: www.nowgen.org.uk

Biomarker discovery: Driving technologies: 28 February 2013
Venue: The Royal College of Pathologists, 2 Carlton House Terrace, London SW1Y 5AF
Contact: enquiries@euroscicon.com
Website: www.regonline.co.uk/Biomarker2012

6th Annual Cell Culture Technology Event: Recent advances, future prospects: 07 March 2013
Venue: The Royal College of Pathologists, 2 Carlton House Terrace, London SW1Y 5AF
Contact: enquiries@euroscicon.com
Website: www.regonline.co.uk/cellculture2013

Forensic Forums: 11-13 March 2013
Venue: The Royal College of Pathologists, 2 Carlton House Terrace, London SW1Y 5AF
Contact: leon.pen@euroscicon.com
Website: http://forensicforums2013.com/

CGS Spring Conference 2013: 14 March 2013
Venue: School of Oriental and African Studies (SOAS), Brunel Gallery, Thornhaugh St, London WC1H 0XG
Contact: bshg@bshg.org.uk
Website: www.clingensoc.org

Proteomic Forum 2013: 17-21 March 2013
Venue: Henry Ford Bau (HFB), Freie Universität Berlin Garystr. 35 14195 Berlin, Germany
Contact: C.Kleinhammer@aon.at
Website: https://proteomic-forum.de/

Advanced European Bioethics Course “Human Genomics and Medical Technology”: 18-21 March 2013
Venue: Study centre Medical sciences, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands
Contact: s.naber@iq.umcn.nl
Website: www.masterbioethics.org

Familial Breast Cancer Family History and Risk Assessment: 20-22 March 2013
Venue: The Nowgen Centre, 29 Grafton Street, Manchester, M13 9WU
Cost: £700
Contact: Online booking: www.nowgen.org.uk/professional-training-events; bookings@nowgen.org.uk, +44 (0)161 276 5956; Further information training@nowgen.org.uk
Website: www.nowgen.org.uk

Mycobacterium tuberculosis......can we beat it?: 21 March 2013
Venue: The Royal College of Pathologists, 2 Carlton House Terrace, London SW1Y 5AF
Contact: enquiries@euroscicon.com
Website: www.regonline.co.uk/tb2012

Venue: The Sands Expo and Convention Center, Marina Bay Sands (MBS), Singapore 018956
Contact: info@hgm2013-icg.org
Website: www.hgm2013-icg.org/index.html
Forthcoming conferences cont...

AGNC Spring Meeting 2013: 15-16 April 2013
Venue: Collingwood College, University of Durham, South Road, Durham DH1 3LT
Contact: bshg@bshg.org.uk
Website: www.agnc.org.uk

Website: www.nowgen.org.uk/professional-training-events; bookings@nowgen.org.uk, +44 (0)161 276 5956; Further information training@nowgen.org.uk
Website: www.nowgen.org.uk

CGG Spring Conference 2013: 22 May 2013
Venue: The Queens Hotel, City Square, Leeds LS1 1PJ
Contact: bshg@bshg.org.uk
Website: www.cggn.org

(ESHG) European Human Genetics Conference: 08-11 June 2013
Venue: Palais des Congrès, 2 Place de la Porte Maillot, 75017 Paris, France
Contact: conference@eshg.org
Website: www.eshg.org/eshg2013.html

Fundamentals of Next Generation Sequencing: 18 June 2013
Venue: The Nowgen Centre, 29 Grafton Street, Manchester, M13 9WU
Cost: Public sector; £190, private sector; £260 (until 31 March); Public sector; £240, private sector; £360 (after 31 March)
Contact: Online booking: www.nowgen.org.uk/professional-training-events; bookings@nowgen.org.uk, +44 (0)161 276 5956; Further information training@nowgen.org.uk
Website: www.nowgen.org.uk

Introduction to Next Generation Sequencing Bioinformatics: 19 June 2013
Venue: The Nowgen Centre, 29 Grafton Street, Manchester, M13 9WU
Cost: Public sector; £290, private sector; £340 (after 31 March)
Contact: Online booking: www.nowgen.org.uk/professional-training-events; bookings@nowgen.org.uk, +44 (0)161 276 5956; Further information training@nowgen.org.uk
Website: www.nowgen.org.uk

The Impact of Genomics on Public Health: 25-26 April 2013
Venue: Radisson Blu Hotel, Cardiff
Contact: BurgessAM@cardiff.ac.uk

Personalised Medicine and Cancer Treatment: 1 May 2013
Venue: The Nowgen Centre, 29 Grafton Street, Manchester, M13 9WU
Cost: Public sector; £190, private sector; £260 (until 28 February); Public sector; £240, private sector; £360 (after 28 February)
Contact: Online booking:

(BSHG) British Human Genetics Conference: 16-18 September 2013
Venue: Arena and Convention Centre, Liverpool, Kings Dock, Liverpool Waterfront, L3 4FP
Contact: Dina Kotecha (bshg@bshg.org.uk)
Website: www.bshg.org.uk

(ASHG) American Society for Human Genetics Annual Meeting: 22-26 October 2013
Venue: Boston Convention and Exhibition Center (BCEC), 415 Summer Street, Boston, MA 02210, USA
Contact: ashgmeetings@ashg.org
Website: www.ashg.org/2013meeting

AGNC Spring Meeting 2013: 15-16 April 2013
Venue: Collingwood College, University of Durham, South Road, Durham DH1 3LT
Contact: bshg@bshg.org.uk
Website: www.agnc.org.uk

Website: www.nowgen.org.uk/professional-training-events; bookings@nowgen.org.uk, +44 (0)161 276 5956; Further information training@nowgen.org.uk
Website: www.nowgen.org.uk

CGG Spring Conference 2013: 22 May 2013
Venue: The Queens Hotel, City Square, Leeds LS1 1PJ
Contact: bshg@bshg.org.uk
Website: www.cggn.org

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Website: www.ashg.org/2013meeting

Agenda...
Happy New Year to all ACC members!

2013 will see the coming together of the largest constituent groups of the BSHG, namely the ACC and CMGS, forming the “supergroup” Association of Clinical Genetic Science. However, unlike many supergroups of a by-gone rock music world, we must view this coming together as a hugely future forward step. This important development is analogous to recent formation of the International Collaboration for Clinical Genomics (ICCG), formerly the International Standards for International Cytogenomic Arrays Consortium (ISCA); bringing CNV and SNV data and collaborations together.

In this brief issue we reflect the end of the era of the ACC with a historical reflection of our successes over the decades by outgoing ACC President, Teresa Davies, together with a look to the future from our out-going ACC Chair (now ACGS Chair) Angela Douglas. We also have a review of the very successful combined ACC/CMGS Spring meeting in Birmingham 2012 (a blueprint for future ACGS meetings?) from Jess Gabriel & Louise Johnston from Newcastle.

You will also find a very important article for all ACC and CMGS members detailing the structure of the ACGS with a call for nomination for positions on the committees and the unveiling of our new logo.

Signing off for the first and final time,

Dom and Sian

Dom McMullan
Sian Morgan

This is probably the last time I will be providing a report for the BSHG Newsletter in my capacity as Chair of ACC. In this period we have seen another major contributor to the Profession, Kim Smith (Oxford) retire. Kim epitomised everything that a Cytogeneticist should aspire to be, a great Leader and true Professional and she will be missed. We wish her every success and happiness in her retirement.

We have also seen the new NHS reforms start to take shape, the new Professional body (ACGS) start to materialise and the implications of the Genomic Review (January 2012) start to play out.

And so to my report:

**ACC/CMGS**

The Professional bodies are in the process of dissolution following an overwhelming endorsement from both memberships. This process is likely to take several months and the Executives (office bearers) of both constitutive bodies continue to meet to take this forward; the last meeting took place on 15th October 2012, in Glasgow, where the process for dissolution was put into action, as you will read from the other articles in this Newsletter.

I have now been appointed as Chair of the Association for Clinical Genetic Science (ACGS), the new joint professional body for Genetics. The official launch of the ACGS is planned for the new style BSHG meeting in the Autumn of 2013, in Liverpool. There will be a one day Heads of Genetic Laboratory Services meeting organised in Spring 2013, to communicate the proposed framework and constitution of the new Professional body and set a strategic plan of work for the next 1-3 years.
Building on the joint workforce reviews performed by the CMGS and ACC, the ACGS will continue to review the laboratory workforce

Human Genomics Strategy Group (HGSG)

This has been re-constituted to implement the recommendations from the Publication of January 2012. Professor Sir John Bell is chairing this group. There are three workstreams working under this Group:

1) Bioinformatics – Met 28 September – David Gokhale and Andrew Devereaux represented Professional Bodies. Angela Douglas and David Baty were invited at the last minute but short notice meant non-attendance. This group looked at the proposal for a Bioinformatics institute and what form this will take, how we create linkages with research and industry from provider organisations and how we store information to provide patients with better access to this information.

2) Service Reconfiguration – A Shared Strategic Framework Workshop hosted by HGSG took place on 7 Nov 2012. Professional body leads were invited to attend this meeting; both David Baty and I attended.

3) Training and Education – Unclear of representation on this meeting clarity has been sought.

A draft proposal will be prepared from the outcomes of these workstreams.

Genetics Education and Training

Only seven STP trainees commissioned in Genetics for 2012 start cohort. Building on the joint workforce reviews performed by the CMGS and ACC, the ACGS will continue to review the laboratory workforce to ensure that there is appropriate and strategic succession planning. The small numbers of trainee scientists being commissioned is a cause for concern.

CSO NIHR Fellowships

Good response from Profession with submissions to the above, we await the outcome of those submissions.

Birmingham Spring Meeting

We would like to thank the Genetics staff of Birmingham Women’s Hospital for organising and delivering a fantastic Spring conference.

They have set an extremely high standard that the ACGS will need to aspire to replicate at future Conferences.

Specialist Commissioned Services Innovation Fund

Just to give everyone the heads up, there is likely to be a call for submissions in January for a Specialist Commissioned Services Innovation Fund; this is likely to be a considerable pot of money £50-£100million up for grabs.

The Criteria that are being considered for submission to this fund are:

- An innovation that is not necessarily a new idea, but new to the NHS
- A new way of doing something
- Something that adds value to the service
- An idea that reduces costs to the system
- An idea that will deliver quality improvement

The fund will focus on ideas that test the effectiveness of a given innovation or evaluate and test an innovation or facilitate the adoption and implementation of an innovation. This will be a three step funded process with the initial step being expressions of interest with a more detailed submission at step two if shortlisted through step one. Step three will involve a more detailed health economics and transformational evidence element.

We need to be considering profession wide projects and with that in mind I will be calling together a group to start scoping potential project submissions. Contact me if you are interested angela.douglas@lwh.nhs.uk.

I would like to thank you all for your support over the past two and a half years that I have been Chair of the ACC, it has been an enormous privilege to have represented you all. I look forward to the next few years and my new role as the Chair of our new joint professional group (ACGS) and look forward to working with you all again, over what is likely to be a really exciting time for Genetics.

And on that note it just leaves me to wish you all a Happy New Year.
Dear ACC and CMGS members

Angela Douglas (Chair of the ACGS and the ACC)
David Baty (Chair of the CMGS)

We are delighted to announce that the constitution, also known as the governing document, for the Association for Clinical Genetic Science (ACGS) has now been ratified by the ACC Council and the CMGS Executive Committee and was adopted on 14 December 2012. A copy of the constitution is now available on the joint ACC/CMGS website for your information (http://www.geneticlabs.org.uk/). The entire membership of both the ACC and CMGS will now become members of the ACGS. The office bearers of the ACC Council and the CMGS Executive Committee continue to work together on the legal aspects involved in registering the ACGS with the Charities Commission and in dissolving the existing organisations. We have submitted all the appropriate documentation to the Charities Commission to apply for charitable status, and are currently awaiting the outcome of that application.

The ACGS will have an Executive Committee and four Subcommittees.

The Executive Committee will have eight members in total. There will be four office bearers: the Chair, the Chair Elect, the Treasurer and the Secretary. The four office bearers will also be the Trustees for the new Charitable Association. The four additional members of the Executive Committee will be the chairs of each of the Subcommittees.

The four Subcommittees will be:
- The Scientific Subcommittee.
- The Quality Subcommittee.
- The Workforce Development Subcommittee.
- The Communications Subcommittee.

Each Subcommittee chair will automatically become a member of the Executive Committee. The chair of each Subcommittee will work with the office bearer of the Executive Committee to deliver the strategic vision of the ACGS. They will be responsible for forming these Subcommittees and for overseeing their themes of work. Each Subcommittee will have a governing document and terms of reference as defined by the Executive Committee and will be accountable to the ACGS, reporting on progress at Executive Committee meetings (three times a year), via their chair. The proposed structure of the Executive Committee is shown below and examples of the remit for each of the Subcommittees, is detailed in the diagram.

In order to register the ACGS as a new Charitable Association, three Trustees had to be in post on the Executive Committee. These Trustees are Angela Douglas, Kevin Ocraft and Nicola Williams. Angela Douglas is the new Chair of the ACGS Executive Committee, as voted by the combined ACC and CMGS membership. To ensure continuity the Treasurer and Secretary will be Kevin Ocraft and Nicola Williams, respectively. The five remaining seats are currently vacant and we are in the process of seeking nominations for these additional committee members. Nomination forms can be downloaded from the joint ACC/CMGS website (http://www.geneticlabs.org.uk/) and should be submitted by the 8th February to Nicola Williams (nicola.williams@ggc.scot.nhs.uk).

Finally, we would like to say a huge thank you to all the ACC and CMGS members who submitted a design for the ACGS logo competition. The standard was extremely high and we were overwhelmed with the quality and the number of designs that were received. We are delighted to announce that Christine Waterman from the Salisbury laboratory won the competition and is now the proud owner of a new iPad. The new logo for the ACGS is shown above.
ACC & CMGS Spring Meeting 2012

Jess Gabriel & Louise Johnston, MSC Pre-registration Clinical Scientists, Newcastle Upon Tyne

This year’s annual ACC and CMGS Spring conference was held in Birmingham; a city famed for its vibrant culture, scientific magnificence… and Jasper Carrott. Geneticists from near and far descended upon the West Midlands, excited about the action packed programme of lectures and workshops that lay before them over the next few days. We were not disappointed!

Day one of the conference got off to a stellar start thanks to Andrew Reid’s Stephen Hawking inspired talk: A Brief History of the ACC & CMGS. Andrew took us on whirlwind journey through genetics starting from the pre-banding era in the 60s, to the introduction of FISH in the late 80s, right up to the introduction of present day technologies such as PCR and sequencing. It was amazing to see how far genetics has evolved over the past 50 years and made us all feel very proud to be working in this area. We were certainly left wondering what the next 50 years holds.

After an excellent opening address, it was back to business with an overview of the Cancer Research UK’s Stratified Medicine Programme thanks to a series of talks from Rowena Sharp, Helen Stuart, Sue Lillis and Pauline Rehal. These were really insightful and gave an excellent introduction to the structure and flow of this program, the successes and challenges faced over the past year and the future aims and goals. Following a brief break for lunch and a wander around the posters and trade stands, it was time to head back into the lecture theatre for the afternoon; once again the programme did not disappoint! Parallel sessions on prenatal diagnosis, bioinformatics and new services were on the menu. Particular highlights included talks from Joan Morris who provided us with a comparison of different screening protocols for detection of Down Syndrome and Michael Cornell who gave a very interesting overview of the diagnostic mutation database (DMuDB).

The day ended with a talk on Genetic adventures in Birmingham by Eamonn Maher.

Day two of the conference began with some interesting talks on prenatal genetic diagnosis. Many of these talks focused on new technologies such as array-CGH, which we are seeing increasingly in a prenatal setting since the advent of the EACH study (Evaluation of Array Comparative genomic Hybridisation and non-invasive prenatal diagnosis using cell free fetal DNA in prenatal diagnosis of fetal anomalies). There was also a talk on prenatal detection of aneuploidy using targeted next generation sequencing. An introduction to the Deciphering Developmental Disorders (DDD) project followed, with the focus of the day turning to developmental disorders and new services. In parallel to these sessions were some haematology talks. Again, the focus was on the introduction of novel techniques using both cytogenetic and molecular genetic approaches. The AML workshop in the afternoon was a brilliant way to highlight both these approaches, and we were lucky enough to hear from established cancer geneticists from the UK and Europe, including David Grimwade. Talks on Tuesday finished in time for us all to attend the much anticipated conference dinner which was enjoyed by all!

New technologies had been the focus for much of the conference and the final day saw this area of rapid growth in genetics at the forefront. We heard talks from individuals from many different laboratories on the use of targeted next generation sequencing technologies for various disorders and referral groups. It was exciting to hear that diagnostic reports are now being routinely issued after work up of such testing strategies. We then heard from guest speaker, Joris Veltmann on de novo mutations in sporadic disease. The afternoon continued with further news of new technologies and their diagnostic applications including talks on quality in genetics, which highlighted issues arising as a result of the increased diagnostic use of next generation sequencing. The final day closed with a prize giving. Congratulations to Chris Buxton, the winner of the best spoken presentation, and Emmanuel Debrand who won the poster prize.

The programme put together by the Birmingham lab was varied, interesting and accessible to both cytogeneticists and molecular geneticists. As MSC pilot trainees, it is fantastic to see the close
A truly exciting era of discovery began. The Human Chromosome Newsletter, an 'unofficial publication' was produced in Edinburgh in 20 volumes between 1961 and 1966, supported by the Medical Research Council. Its aim was to circulate information on the new discoveries and important technical advances in the field of human cytogenetics, and attracted submissions from as far afield as Mexico, India, USA, Italy, Czechoslovakia, USSR as well as UK.

The 1970s saw the next great breakthroughs with the development of banding techniques, and structural abnormalities which were described in large numbers. The concept of the micro-deletion or contiguous gene syndrome was born with identification of Prader-Willi, Angelman, Smith Magenis, Miller Dieker and Di George (VCFS) syndromes. The 'fragile X' chromosome first noted in 1969 took till the late 1970s before cytogenetic analysis for fragile sites became routine by culturing cells in a folate deficient medium. The next big leap came in the 1980s with fluorescent in situ hybridization (FISH). The 1990s saw comparative genomic hybridization (CGH) and later microarray technologies, further blurring the traditional distinction between cytogenetics and molecular biology and changing the nature of cytogenetics.

The 1960 Denver Conference attempted to classify chromosomes based on size and shape. Since 1963, The International System for Human Cytogenetic Nomenclature (ISCN) has served as our reference for describing human chromosomes. The latest edition, recently published, includes new definitions such as ‘chromothripsis’ (I had to look this up!).

The imminent coming together of the Association for Clinical Cytogenetics, ACC (formerly Association of Clinical Cytogeneticists) and Clinical Molecular Genetics Society, CMGS into the Association for Clinical Genetic Science (ACGS) is a time to glance back and recognise our enormous achievements and how we got to where we are today. This is far from a comprehensive history, merely a snapshot. It is a personal selection which it is hoped will be of interest, inform and entertain - apologies for errors, they are entirely my own. Extracts are taken from documents in the ACC archive collection which are currently in my spare room but will shortly be deposited at the Wellcome Library archive. (The ACC website archive is already held there www.webarchive.org.uk).

Firstly, the ACC is not a ‘thing’ but is made up of its members. Many, people (too numerous to mention) have contributed, not just by sitting on Council and countless other committees but also in working parties, submitting data, presenting science, delivering training, study days, examinations, professional standards, quality assurance, bringing back and adopting new ideas to their own service. Thank you to all.

The early days of cytogenetics began long ago in the 1840s when thread like structures were first described in the nuclei of plant cells, later (1888) called ‘chromosomes’. Many years later sexing using the Barr body was described (1953) and in the 1950s technical improvements led to the establishment of 46 as the correct number of human chromosomes in 1956 (the year I was born!). This was the start of enormous activity and interest in clinical cytogenetics.

The working relationship of what are historically separate disciplines, and it seems clear that with the introduction of new technologies, diagnostic genetics is moving towards working as one. This is reflected by the now approved dissolution of the ACC and the CMGS, with work being done to establish our new joint professional body, the Association for Clinical Genetic Science. This is certainly an exciting time for diagnostic genetics.
Quality has always been at the forefront of practice

The ACC began when the constitution of the Association of Clinical Cytogenetics was registered with the Registrar of Friendly Societies as a “specially authorized society for the advancement of science” on 16 May 1978.

The first ACC AGM was held on 2 May 1979; Dr Charles Ford became the first Honorary Fellow and President. There were 101 members and a bank balance of £160. The Guest lecture, by Professor Paul Polani was Chiasmamta, nondisjunction and female meiosis. Before the AGM itself, there was luncheon, coffee and wine, all for £2.50 (future organiser please note).

A history of the ACC was published by David Townsley-Hughes and Mike Creasy in the BSHG November 2003 Newsletter for our 25th Anniversary.

Within a very short period of its establishment the ACC made considerable achievements being recognised, for example, in the Department of Health, and the Whitley pay machinery. The salary in 1980 for a Scientific Officer was £4125-5817. Whitley was modernised into Agenda for Change, agreed in 2004, along with National job Profiles, KSF and other improvements!

Items discussed in the first (and many subsequent) Council meetings included training, registration, science and technologies.

Education, training and examinations were regarded as essential from day one. Study days have taken place for many years, although the content has changed. The first was a workshop The origin and inheritance of numerical and structural chromosome abnormalities held at the Cytogenetics Laboratory in Birmingham. Other events helped prepare candidates for the examinations such as the Taunton courses, (fondly remembered for the table-tennis and quizzes). The first examination in Clinical Cytogenetics was held in September 1983; in 1988 this became ‘Clinical Cytogenetics and Molecular Genetics’. This was later replaced with DipACC then DipRCPath (Part 1) and full Membership (later Fellowship).

The ACC Bulletin followed in 1982 (until 1994) and was issued free to all members.

The successful National Supernumerary A grade Clinical scientist training scheme was formed, supported by National Assessors, and the ‘Training for Trainers’ course and was soon followed by training programme for Genetic Technologists. All the expertise gained from these being recognised with genetics leading the way as the pilot for Modernising Scientific Careers.

The first National Scientific meeting was held in 1983 at the newly opened Duncan Guthrie Institute for Medical Genetics, Glasgow. The guest speaker was Professor H. J. Evans who gave a talk entitled “Genes, Oncogenes and Cancer”.

Ten years topics included: Confined Placental Mosaicism; Trisomy Rescue and Uniparental Disomy for Chromosome; The diagnosis of Acute Promyelocytic Leukaemia using RT-PCR; Fishing for 22q11 deletions as a diagnostic service, and CGH for the Molecular Cytogenetic analysis of Solid Tumours.

The ACC Scientific Committee contributed a number of Working parties. The ACC has also contributed data to areas like the National Down Syndrome Register which started in 1989.

Workforce issues were also tackled by the ACC with reviews of workforce skill mix and the collection of detailed workforce data for many years. The first Review of Staff Structures and Services in Cytogenetics Laboratories was published in an ACC report in 1989 and a follow up report in 1996.

Quality has always been at the forefront of practice and a pilot quality assessment scheme was set up in 1982 by the ACC. In 1983 the Scheme was recognised as an External Quality Assessment Scheme in Clinical Cytogenetics (UKNEQAS). The first ACC professional guidelines were published in 1994 with the ACC/NEQAS Guidelines for Clinical Cytogenetics followed by Professional Guidelines for Clinical Cytogenetics (ACC 2001) and subsequent reviews and additions in response to services development including Best Practice Guidelines produced jointly with CMGS – QF- PCR for diagnosis of aneuploidy (2007).

The Clinical Pathology Accreditation (CPA) company was incorporated in 1992 first for accreditation of medical laboratories, and then extended in 1996 to EQA Schemes. Cytogenetics
When the ACC was founded it had 101 members – there are currently over 600 members

Laboratories have led the way and were among the first to be accredited. CPA has evolved with new jargon to be learned and standards reviewed and revised.

The need for professional registration was recognised early on by the ACC. Progress was slow but in 2001 registration for Clinical Scientists was achieved with the Council for Professions Supplementary to Medicine (CPSM). The CPSM itself was replaced by the Health Professions Council on 1 April 2002, which then became the Health and Care Professions Council on 1 August 2012.

Data management has always presented us with challenges. A two-day ACC Computer appreciation course was held at Sheffield in 1982. It was concluded that the "multiuse microcomputer was the only answer". We eagerly await the ideal system being developed as we struggle with bioinformatics and a mindboggling complexity of data.

Automation was discussed in the 1983 ACC Bulletin with the report of the use of Television as a visual aid for cytogenetical diagnosis with a magnification of 7400x. Further automation came along with robotic harvesting of cell cultures using the Hamilton 2200 sample processor presented at the 1992 scientific meeting.

DNA and Molecular Genetics featured at early ACC meetings with topics such as The locus for Cystic Fibrosis (1984). In 1987, the aim of the ACC was updated to include 'the advancement of clinical cytogenetics and its molecular aspects'. The CMGS constitution was adopted in 1988 and became registered in 1999 with charity commission. 2002 saw the establishment of the UKGTN Steering Group and 2003 the Genetics White paper established 'Our Inheritance our Future'.

The British Society for Human Genetics (BSHG) was formed in 1996 from the coming together of ACC, CMGS, Clinical Genetics Society and Association of Genetic Nurses & Counsellors, giving human genetics a bigger voice and everyone access to combined meetings and newsletter.

The increasing close link with CMGS that has continued over the years has led us to the natural progression to a formal coming together of the two groups into the new ACGS.

When the ACC was founded it had 101 members - there are currently over 600 members. The total genetics laboratory workforce from laboratories submitting data for 2011-12 is over 1300 individuals. Together we have an even bigger voice to shape the future of clinical genetics laboratory sciences.

In conclusion
I am very proud to have been part of a profession that has contributed to the development of the exciting science of human genetics and the responses to the many challenges laboratories have faced, sometimes going in circles before moving forward. Clinical Cytogenetics and the ACC have a long history of responding with innovation, creativity, commitment and co operation. A history to be proud of and which will stand it in good stead to face the many challenges to come.

Good bye ACC, Hello ACGS – the future awaits – go for it ………….and good luck to all.

Contributions for the next issue will be through the Communications Subcommittee of the ACGS

Deadline for contributions for next issue is 30 April 2013

ACC News Guest Editors
Dom McMullan
West Midlands Regional Genetics Laboratories
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Editorial

Getting the Message Across – a new book about improving communication in clinical genetics


We have just published a book called: Getting the message across: communication with diverse populations in clinical genetics. The inspiration for the book came from the AGNC session at the 2008 BSHG conference – all the presenters were experts in their field and delivered practical presentations about how to communicate effectively with specific patient groups. We invited these presenters as well as experienced genetic counsellors from across the UK to write chapters. We asked them to think about the advice they would give colleagues if they were being shadowed in a consultation. The net result is a fascinating, experience-led narrative; each chapter has case studies and bulleted summaries so it is easy to dip into.

We particularly wanted the book to be relevant for genetic counsellors preparing for registration as well as to experienced genetic counsellors and geneticists who wanted to have a quick read-up about a particular client group before a consultation. The chapters cover the following topics:

- Working with clients who are D/deaf or hard of hearing, visually impaired, or are affected by diverse sex development.
- Clients from the Jewish community, the Traveller community and from the Pakistani Muslim community.
- Clients who disclose sexual abuse, who are teenagers, children who have intellectual disability, clients who are terminally ill or who have dementia.

We also have chapters focusing on working with interpreters and counselling by telephone.

Getting the message across: communication with diverse populations in clinical genetics will be available from spring 2013.
This is my first report to the BSHG newsletter following my appointment to the AGNC committee. Thank you to all of you who voted for me. I will do my best to serve all your interests and look forward to being involved in what is really a challenging but also exciting future ahead for those of us who work in genetics. Also thank you to the AGNC committee who have really taken me under their wing.

Recently we have had two stimulating and interesting meetings, the first a joint AGNC and lead counsellors meeting, then followed closely by an AGNC committee meeting, both kindly held at Great Ormond Street Hospital and I would like to thank Anita Bruce for her skill and patience in organising these two days. It is always invaluable to obtain a perspective on how all our centres are functioning and the positives and dare I say it, negatives, from around the country.

The genetics landscape is always changing and we quickly move on to the next challenge. However, on observing colleagues talk and present on different aspects of our profession, I am in awe of what we have already achieved that we need to congratulate ourselves. Having been in genetics now for many years, the development and expansion of the AGNC itself, focus on our professional roles, setting up a career structure, development of the registration process, training, supervision and exploration of a regulatory framework have only been possible because of the dedication and enthusiasm of AGNC members. The setting up of the Genetic Counsellor Registration Board (GCRB) and the Joint Committee on Genetic Counsellor Regulation (JCGCR) have been huge steps forward in establishing and developing our profession. It is also clear that we are fully included in the debates and discussions regarding future developments within genetics.

However, it is also important that we continue to move forward and discussions at the AGNC committee meeting were focused on how we do this. We are faced with the challenge of continuing with training for colleagues who would like to enter the profession as funding for trainee genetic counsellors comes to an end from the Department of Health and need to think creatively about clinical training. We are also aware of developments in exome and genome sequencing and the mainstreaming of genetics and new specialist commissioning plans, which will undoubtedly have an effect on our practice. The AGNC committee is involved in discussions and working with our colleagues within BSHG regarding these developments and will share information with our members as we learn more.

The AGNC spring meeting is on the 15 & 16 of April and is being hosted in the wonderful city of Durham and I am sure will be full of stimulating and exciting presentations. Donna McBride and Phona MacLeod are on the scientific committee for the BSHG conference next year and whilst it is a long way off on the 16, 17 & 18 September, we are planning the speakers now for the genetic counselling sessions and am sure you will be pleased with the speakers we will have for you.

A reminder to genetic counsellors and nurses new to our profession. The new genetic counsellor e-mail group is up and running and information regarding this group can be found on our website. Also a reminder that we do offer travel awards for AGNC members, so please do apply. Details are on our website. We are in the process of redesigning the AGNC website and Anita Bruce and Liwsi Kim Protheroe-Davies have been instrumental in developing a website I am sure you will all be pleased with. Hopefully this will be launched early this year.
November 2012 Update
Aoife Bradley, Belfast, (on behalf of the GCRB)

Registered Genetic Counsellors – Renewal of registration in 2012
Glen Brice Ann Kershaw
Sarah Buston Cath Knightley
Tara Glancy Caroline Kirwan
Lorna Day Mark Longmuir
Catherine Falconer Lorna McLeish
Selina Goodman Christine Patch
Rachel Hardy Sarah Pugh
Catherine Anaar Sajoo
Houghton Sarah Smalley
Chris Jacobs Judith Tocher
Charlotte Jaggard Jessica Williams
Lisa Jeffers Catherine Willis
Rosemarie Kelly

Evaluation of New Assessment Process
The GCRB are pleased to announce the results of our first ever comprehensive online evaluation from those involved and taking part in the second cohort of the New Assessment Process. The results were collated and evaluated independently of the GCRB by Melissa Hillier from Genetic Alliance UK. The vast majority of feedback was either satisfactory or very satisfactory. Key areas for improvement include:

• Increasing access to the Board Moderator on marking day, and improving the quality of applicant feedback. The board have arranged for the Board Moderator to have additional support on the marking day from the Past Board Moderator each June. We have developed a Feedback Guide for Assessors, and will continue to write personalised results letters and aim to increase awareness of access to Board members for one to one discussion. The results of the evaluation will be published online following the Board meeting in January 2013.

New Assessment Process Reminders
• Minor amendments no longer exist. In the old process, all applicants were required to make a number of minor corrections to portfolio content, to be submitted three months later even if work met Masters Level (MLevel) standard. This was very challenging to administer in such a tight time frame, and unfair to applicants who had met the standard. Deferrals in the new process are the equivalent of major amendments in the old process (i.e. an aspect of work does not meet MLevel standard). Resubmissions are given priority, and applicants will be notified of the outcome as soon as possible, before the June marking day.

• Deferrals = Registration in Progress, not failure. A Fail means that a whole new portfolio must be submitted along with another fee. We encourage Sign-Off Mentors (SOMs) and applicants to discuss what a deferral means and how they will manage should this situation arise prior to submitting the portfolio. In future, we will refer to this situation as “Registration in Progress” not “Deferral” which is an opportunity to bring area(s) of work up to MLevel standard, without having to resubmit a whole new portfolio.

• Scholarly Writing Style is assessed. As in the old process, the portfolio should be free from typographical and grammatical errors, and content should be well structured. Unsatisfactory writing style may cause a deferral if other parts of the same work are assessed as Not Satisfactory. Please see ‘Assessment form’ under ‘Assessors’ on the GCRB website for marking criteria.

Maternity Leave/Sick Leave and Continuing Professional Development (CPD) Policy
A minimum of 30 hours CPD per year is required, irrespective of the hours worked. However, if an applicant has been away from the workplace for a statutory reason (e.g. maternity leave or long-term sickness) these 30 hours/year can be redistributed so that there is an average of 30 hours/year, but >30 hours should be in the year before and after the leave. A GC will still be expected to have at least 30 hours (CPD) in the year preceding submission of Intention to Register. If any applicant is unsure about meeting the requirements they should seek the advice of the GCRB for guidance on the number or ratio of CPD hours required.

Electronic Fee Payment
The board is in the process of arranging a new company bank account, which we have been informed may enable us to move from cheques to electronic bank transfer for Registration and Renewal fees. Our Company Secretary is on the case, and we will keep everyone updated.

Change in Board Membership
The GCRB would like to announce a change in membership. In January 2013 Jan Moore, Aoife Bradley and Lesley Snadden will have completed their terms on the GCRB. We are very grateful to Jan, Aoife and Lesley for their work, enthusiasm, contribution and dedication to the GCRB. We look forward to working with Caroline Benjamin, Cathy Watt and Jennifer Wiggins who are joining the GCRB in January 2013.

Feedback
The GCRB welcomes your views and suggestions. Please contact the Board Administrator at cabarnes@blueyonder.co.uk or any GCRB board member.
Profile of Northern Genetics Service - Genetic counselling team

Kathy Barnes, Middlesbrough (Teesside)

The Newcastle service was established as a comprehensive unit in the early 1980s by Professor Sir John Burn. It was originally based in a Georgian House near the Royal Victoria Infirmary, but as the unit developed and grew it was given a new home in The Centre for Life in 2001. 2003 saw the opening of the satellite Teesside Genetics Unit, based at James Cook Hospital in Middlesbrough.

Cytogenetic and Molecular Laboratories are based in Newcastle at The Centre for Life. Specialist testing for neuromuscular and mitochondrial disorders is also offered on this site.

The service has a specialist muscle team. This is a clinical and research team providing services locally, nationally and internationally to patients with rare inherited neuromuscular diseases.

The Northern Genetics service covers a population of approximately three million, from Northumberland to North Yorkshire, as well as the northern half of Cumbria (see map). Most patients from Northumberland travel to clinics in Newcastle. Clinics are also run in Gateshead, Washington, Sunderland, Chester-le-Street, Peterlee, Hartlepool, Bishop Auckland, Darlington, Middlesbrough, Northallerton, Carlisle, Whitehaven, Workington and Penrith.

Currently there are 9.5 WTE NHS Consultants and Dr Paul Brennan is the clinical director.

There are 11 Genetic Counsellors equating to 8 WTE:
- Lindsay O’Dair, Lead Genetic Counsellor RGC
- Oonagh Claber, Lead Genetic Counsellor RGC (Teesside and Newcastle)
- Gill Brigham
- Dr Lorraine Cowley, PhD RGC
- Susan Fairgrieve RGC
- Sharon McDonnell RGC
- Catherine Prem RGC
- Kathy Barnes RGC (Teesside)
- Gill Brigham
- Dr Lorraine Cowley, PhD RGC
- Susan Fairgrieve RGC
- Sharon McDonnell RGC
- Catherine Prem RGC

There are currently 12.5 WTE support staff: They provide follow up care to patients with genetic muscle disease and NF. This includes an annual follow up service for patients with Myotonic Dystrophy. One nurse is responsible for cancer triage coordination in the northern part of the region.

Specialist Nurses:
- Louise Hastings (Muscle)
- Claire Pickthall (Muscle)
- Susan Musson (NF)

Genetic Associate:
- Trish Williams (Cancer Triage, Newcastle)

Teams of Administrative support are at both units.

All genetic counsellors work independently, generically and largely geographically. Caseloads are therefore varied and challenging. However each principal GC also has an area of special interest in which they take a lead role, for
example, HD, Prenatal, Neurology but as all cases are treated generically, expertise is constantly extended and developed. Most general cases are brought straight to clinic, cancer cases are ‘worked up’ before appointment. Home visits are offered on the basis of clinical need, in the more outlying areas this can be quite a challenge!

Co-counselling takes place in a few specialist clinics (skeletal dysplasia clinic for example) but is otherwise only offered after discussion between Consultant and GC where it is thought that it might be beneficial to all parties.

Departmental Clinical Meetings take place twice a month. Genetic Counsellors also have Supervision on a monthly basis.

The Teesside Unit works closely with The Cancer Family History Service which was established in 2004 initially funded as part of a Macmillan-DOH project. It is now an independent service funded by local Primary Care Trusts and supported by Macmillan. All cancer referrals in the southern part of the region (population 1.1 million) are triaged and assessed by the GRAPS (genetic risk assessment practitioners). Moderate risk patients are seen in the GRAP clinics and high risk are referred to the Genetics Team. The GRAP assessment tool has now been adopted by The British Heart Foundation Cardiac Team which covers all of the Northern area and makes similar appropriate referrals. Both these teams liaise very closely with Dr Brennan and the genetic counselling team.

Don’t forget – the AGNC Conference, 15 -16 April 2013 in Durham!
The Genetic Counsellor Training Post (GCTP) scheme

Judy Tocher, Sheffield

The GCTP scheme, funded by the Department of Health (DH) is nearing an end.

- Of the nine trainees in the jointly-funded third phase of the scheme, four have obtained substantive genetic counselling posts and two have completed their training very recently and are seeking employment as a genetic counsellor. The remaining three trainees are scheduled to finish their posts in 2013.

- Of the 43 trainees appointed in the first two (fully DH-funded) rounds of the scheme, 42 went on to work as genetic counsellors, of whom 38 have already gained professional registration with the GCRB.

- Recently, an article about the GCTP scheme, including its historical background and outcome data, was published in the Journal of Community Genetics. The reference is as follows:


The Panel hopes that the publication may be of help to international colleagues who are in the process of developing genetic counsellor training in their own countries.

Locally-funded training posts and approval of training centres.

The GCTP Panel, the AGNC Committee and the Genetic Counsellor Registration Board (GCRB) remain committed to the continuation of structured training posts and approval of training centres. Although the DH funding for training posts is now at an end, the Panel remains committed to offering structured support to Centres who continue to employ trainee genetic counsellors. To this end, the Panel is very keen to hear from those centres who fulfill the criteria for an approved GC Training Centre (or are interested in finding out more about such approval), and have a training/Band 6 post in their department. All enquiries about this can be sent to Chris Barnes.

The future

Not only is the Panel committed to supporting Centres with their efforts to embed recurrent training posts in their department, it is committed to exploring avenues for future structures and funding to ensure the continuation of high-quality genetic counsellor training in the UK. To this end, the Panel have contacted all genetic centres to canvas information about local situations, views and ideas.

GCTP Membership

Judy Tocher has taken over as Chair of the GCTP Panel, and Chris Barnes will continue to act as Panel Administrator (as well as Panel member until the end of 2012). They are delighted to welcome new Panel members Claire Dolling, Sue Kenwrick and Rhona Macleod.

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<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Judy Tocher (Sheffield) (Chair)</td>
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<td>Chris Barnes (London)</td>
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Two GCs and a poster abroad: Postcard from Nuremberg
European Meeting on Psychosocial Aspects of Genetics (ESHG/EMPAG) 23rd–26th June 2012

Jan Birch, Liverpool

There were many interesting presentations too numerous to relate, however sessions which particularly stood out included Saturday evening’s plenaries. Milena Paneque Herrera’s paper from Portugal gave a valuable account of the patient’s perspective on what is successful in genetic counselling for presymptomatic testing. She gave us food for thought in these days when endeavours to improve efficiency can sometimes question the number of patient appointments. The important question we should ask ourselves as clinicians about our practice with this group of patients is ‘Are we safe?’ Despite a very long day Sasha Henriques kept our attention right until the last moment with Manchester’s paper on the particular impact of predictive testing on young people. The subsequent discussions continued way on into the night at the networking reception and it was great to be able to compare different practices internationally.

The six speakers at Sunday’s plenary on ‘Reproductive issues and newborn screening’ highlighted current issues for patients and clinicians including some of the benefits and disadvantages of non-invasive prenatal diagnosis from the patient’s perspective. Patients found the experience of having a non-invasive test psychologically easier as there is no visual acknowledgement of the fetus. However, if the pregnancy miscarried and fetal sex was known, they felt worse psychologically, whatever the sex of the baby and the issues around testing. Although ‘disengagement’ with the pregnancy started earlier, thus in some circumstances was prolonged, patients also commented that the timing of taking a non-invasive test allowed them time to prepare to make decisions about their pregnancy if this scenario arose. Highlights of Monday’s joint workshop included Leigh Jackson’s presentation which generated topical discussion on the

Reproductive genetics and hotdogs - well organised signposting

Gail Mannion and Jan Birch at the Networking Reception NCC Ost
Conference Information: Genetic Haemochromatosis Benchmarks
28 February 2013, London

Registration bookings may be made either online at the Association for Clinical Biochemistry (ACB) Website (www.acbstore.org.uk/site/index.aspx) or through the ACB Administrative Office (enquiries@ACB.org.uk)

dilemmas in clinical practice of dealing with incidental findings on microarray, a subject with which many of us are becoming familiar.

Social networking on Sunday focused on the football and as we watched England lose to Italy we drowned our sorrows thankful that we had attended the vitamin breaks that were interspersed throughout the programme. The congress party in the Meistersingerhalle was another chance to network and to compare international dance moves. The band even asked the important research question “Are we human, or are we dancer?”

Tuesday was a day of reflection both on the risks and benefits of a free bar and on the success of the conference. Poster viewing and exploration of the interesting exhibition stands was continuous throughout the conference and thankfully plenty of coffee was on hand. This was our first experience of an international conference and we would definitely recommend EMPAG. It was refreshing to hear so many thought provoking presentations giving the patient’s perspective of being on the receiving end of genetic counselling. There was not a great difference in cost of travel and accommodation compared to a three day UK conference. We met some lovely people from all over the world and will definitely continue to try to broaden our horizons in the future.

With thanks to the conference organisers and contributors and special thanks to the AGNC for their support of an International Travel Award of £300 for me to attend this conference, also for their commitment to enabling Genetic Counsellors to present their work nationally and internationally.
Editorial
Natalie Canham, KGC

All is changing in the wonderful world of genetics commissioning, with the advent of national (England-wide) commissioning, mainstreaming and dashboards. Of course, at the time of writing details are not clear or, apparently, even decided. Perhaps by the time of publication the mists will be slightly clearer as the cliff-edge of April 2013 approaches. I am grateful to Alastair Kent, of Genetics Alliance UK, for putting the patients’ view of the challenges and potential pitfalls of this reorganisation.

All has already changed in Clinical Genetics training, with the first two guinea-pigs having already taken the Certificate in Medical Genetics examination, and more to come next spring. I’m sure that I am not alone in feeling fortunate that this particular hurdle was not in my way during training, but evidence of knowledge and ability is always important, and becoming more so with revalidation looming on the horizon. The CGS beneficence also continues to make its mark, and I was pleased to receive two reports from recipients of the Travel Scholarships. Be warned all of you who have not yet written your reports – I’m after you!

All is also changing in the virtual world, and Shane, one of our more computer-literate colleagues, has shared his knowledge of Twitter with us. From personal experience I can tell you that it can take up a large part of your life, but if you actually subsequently acquire a life in the real world, it fades into the background somewhat. Of course it is very likely that Shane will let me know that I’m just not using it properly…

Delivering integrated care for patients with rare genetic conditions - commissioning strategically
Alastair Kent, Director, Genetic Alliance UK

Lessons from History
To date, the NHS has had a patchy record when it comes to delivering high quality care for patients and families with rare genetic conditions. In England those affected by some of the ultra rare disorders (affecting fewer than five hundred), and fortunate enough to have the support of either an active patient group, a pro-active group of expert clinicians, or both, have been able to make a case to the National Specialist Commissioning Team (NSCT) and the Advisory Group for National Specialist Services (AGNSS) for directly commissioned services organised and funded at national level. Those affected by more common conditions, and those where there is no clear consensus on what constitutes high quality care, have had to rely on Regional Specialist Commissioning Groups (RSCGs). As a consequence, access to services and support has varied, with geography often seeming to be more important than clinical need as a determinant of access. Different arrangements operate in Scotland, Wales and Northern Ireland, making it difficult for patients to know what they can reasonably expect from the NHS.

An Opportunity to Improve
The reorganisation of the NHS in England, the establishment of the NHS Commissioning Board (NHS CB), and the commitment from the UK government and those of the other home nations to formulate a National Plan for Rare Diseases has created an opportunity for addressing the inequalities inherent in the current system, and building a framework that delivers uniformly high quality integrated services to patients and families wherever they live in the UK. Grasping this opportunity will require leadership, and a willingness to work together in the interests of patients and families, from commissioners and providers. It will also be crucially dependent on developing opportunities for systematic input from those directly affected by these conditions and their carers.

National standards for services that reflect patient needs and expectations, and which include relevant and verifiable outcome measures, will need to be established and implemented if patients’ needs are to be met, and the effective use of scarce expertise and limited resources is to be justified. Country-wide commissioning creates the opportunity for levelling up. It also allows for system-level recognition of where expertise is actually to be found, and for patients to access this when they need it, wherever they live in the UK, through cooperative measures across the four NHSs. Pressure on resources also generates the threat of levelling down, notwithstanding the fact that a lower quality service can be more expensive due to
wasted time and money spent on ineffective, irrelevant or even harmful interventions. Genuine patient engagement will help to counter this threat. Patients and families know what bothers them most about their condition, and what works when addressing these issues. They are not usually unrealistic in their expectations, even if their aspirations may currently be out of reach due to limitations in current scientific understanding and/or clinical possibilities.

The NHS CB, opportunity or threat?
Given that the NHS in England is undergoing the most radical reorganisation for decades, what do patients and families expect from this process?

1. **Transparency.** The Board must be open about the framework it uses to decide priorities, the weights it gives to different stakeholder inputs to the process and the constraints - whether political, financial or due to a lack of knowledge and expertise - to its freedom to act.

2. **Robustness.** The model the Board uses to reach decisions needs to be based on a logical framework derived from hard evidence. This needs to carry the support of those on whose behalf the decisions about service specifications and resource allocations are being made.

3. **Comprehensive.** All relevant information needs to be taken into account, not just those bits which support the predetermined ‘right answer’. Cherry picking should not be an option.

4. **Equity.** The basis for deciding between diseases and across regions must be such that the founding principles of the NHS are clearly taken into account. No patient should feel they are too rare, too difficult or too expensive for the NHS to make a response to their needs.

5. **Appealable.** No system is perfect, and if patients feel the system has made a mistake then they need to be able to challenge the decisions taken on their behalf. Even if the challenge is ultimately rejected, while they may not be happy with the result, they will be more likely to feel they have had a fair crack of the whip.

If these principles can be incorporated into the decision making and commissioning framework of the NHS CB then there is the basis for sustainable patient and public confidence in the legitimacy of the underpinning for Board allocation decisions. If they are not, then the anxieties of patients about privatisation and exclusion are likely to be reinforced, no matter how vociferous the denials from officials and politicians may be.

The way ahead
In a time of change there is a risk that divide and rule will be the order of the day. To avoid this it will be essential that all those who cling to the ideal of an NHS that truly reflects the vision of its founders, and which is able to incorporate these into new ways of working that reflect current good practice and respond to emerging knowledge and scientific progress, work together to articulate a coherent vision for the delivery of sustained progress towards the meeting of health needs of all patients, including those with rare and complex genetic disorders. This is a goal we can all share, no matter what our starting point might be.

alastair@geneticalliance.org.uk

Having enjoyed my experience of dysmorphology so far I was very pleased to have a poster accepted for the 15th Manchester Dysmorphology Conference. The conference runs over 4 days and I was most grateful to the CGS for the scholarship towards the costs of attending the meeting.

My poster described a fascinating family with an OTX2 mutation resulting in a varied phenotype including ophthalmic, endocrine and neurodevelopmental features. Many of the features have been described but the most severely affected child had a nasal cleft which had not previously been reported.

The conference was attended by an international audience of dysmorphologists, some of whom have attended every conference since its inception. The result was an exceptionally high quality series of presentations and posters. As a junior trainee I was somewhat in awe!

The first session was excellent and included two presentations about Cantu Syndrome. Ingrid Scurr presented the clinical spectrum of features in a cohort of Cantu patients, and this was followed by Mieke Van Haelst’s talk about the identification of ABCC9 as the cause. This pair of talks gave a lovely demonstration of a clinical syndrome and how one gets from the syndrome to the causative gene. What was also fascinating was that in this particular case there are exciting therapeutic possibilities which can be neatly explained by the molecular mechanisms.

Jill Clayton-Smith presented the phenotypic spectrum associated with KAT6B in the Ohdo-Say-Barber-Biesecker
identified the 40 individuals in whom they have now clinical features that have been seen in clinically oriented talk and described the Weaver syndrome. This was a fantastically the clinical and mutational spectrum in Kate Tatton-Brown presented her work on which including with genitopatellar syndrome in overlap in the clinical phenotypes KAT6B mutations have also been described.

Kate Tatton-Brown presented her work on the clinical and mutational spectrum in Weaver syndrome. This was a fantastically clinically oriented talk and described the clinical features that have been seen in the 40 individuals in whom they have now identified EZH2 mutations. Some key points for clinical examination were that it appears that birth length is more important than birth weight and that there is a massive variability in head circumference. Some have a normal head size but most were above the 50th centile.

The many clinically oriented talks about the spectrums seen in conditions, which included Cornelia de Lange, Simpson-Golabi-Behmel and Coffin-Siris, were very helpful to be able to take back to clinical practice, but what also came across throughout the conference was the rate of advance of technology and the amount of new information that is coming out of the use of exome sequencing in rare genetic conditions. The conference was a great educational experience and has certainly inspired me to continue with my interest in this area. It remains to be seen what role we will have as dysmorphologists in the years to come, but this conference has convinced me that while the role may be slightly different and our approach may change with the advances of technology the need will be just as great.

As an ST4 trainee in Leeds, I have had the opportunity of spending 6 months of my training focusing on cardiac genetics alongside our dedicated cardiac genetics team, who provide weekly multi-disciplinary clinics, accessible to patients from across West and East Yorkshire. During my training, I have developed an interest in cardiovascular genetics, and in particular, an academic interest in the cardiomyopathies, a group of conditions with complex pathogenesis, variable presentation and potentially devastating consequences.

Until recently, genetic testing for Hypertrophic Cardiomyopathy (HCM) in Leeds was outsourced to external laboratories. For just over a year the Yorkshire Molecular Laboratory has been providing a basic panel of genetic testing for HCM, using massively parallel sequencing. In close collaboration with our laboratory team, I carried out an assessment and audit of the service transformation associated with the provision of in-house next-generation sequencing (NGS) and have explored the impact on cost, efficiency and accessibility.

I was delighted to be awarded the CGS travel scholarship to present this work at the 2nd Florence International Symposium on Advances in Cardiomyopathies held on 26-28 September 2012. This was a great opportunity to present at an international meeting and to advance my knowledge in this field, aided by experts from around the world.

To commence the conference, Dr Perry Elliot discussed the difficulties in developing a single classification system for cardiomyopathies, when the utility of such a system will depend on the user, be it cardiologist, geneticist or scientist. He stressed the importance of a systematic approach to differential diagnosis and the rising profile of genetic analysis in assessment. This was complemented by Professor Bonow’s talk comparing perceptions and practice in the USA and Europe, providing a global perspective.

A personal highlight was the session on genetics in clinical practice. This provided important messages on the likely impact of next-generation and whole exome sequencing in clinical practice, and the major challenges which lie in analysing and interpreting the new complexity of data. Presentations by both Dr Lopes and Dr Girolami highlighted the importance of good phenotypic knowledge of the patient and their family to aid variant interpretation and segregation analysis.

Professor Mestroni gave a presentation summarising the recent advances in Dilated Cardiomyopathy (DCM). More than 40 genes are now known to be associated with DCM, most with low frequency. She discussed the exciting recent discovery of truncating mutations within the TTN gene, which were found in 25% of patients with familial DCM.

I would like to thank the CGS for the opportunity to attend and present my work. This conference was an excellent educational experience, providing insight into the exciting recent advances in the aetiology of cardiomyopathies, the growing genetic complexity, overlapping phenotypes and the challenges of patient management. I left with a clear insight into the importance of expert collaboration between international centres, combined with expertise from clinicians and scientists of multiple disciplines.
Keep Calm and Carry On

Peter Turnpenny, President, CGS

The phrase might also be an apposite reflection on a short transatlantic tête-à-tête that was published recently in the American Journal of Medical Genetics. Tabor et al. first highlighted potentially new ethical challenges posed by exome (ES) and whole genome sequencing (WGS) in human subjects, which elicited a response from Christenhusz et al., who argued that ‘filters’ should be applied and that only data which is clinically useful, after WGS analysis, should be reported and communicated. Tabor and Bamshad rounded strongly on this view with their “The sky won’t fall” response, arguing that the application of filters in ES/WGS reporting would be very shortsighted.

There probably has not been such a buzz around a new genetic technology since karyotyping was first introduced in the late 1950s. We are excited, but at the same time a little apprehensive, and as I write this we are less than a week from the Prime Minister making a significant announcement on new genetic technologies and innovation. At the BSHG Conference in September the Great Debate homed in on the evolving role of the Clinical Geneticist in the forthcoming era of ES/WGS. The motion, "This house believes that the art of clinical phenotyping is now redundant", was defeated, but there was something of a moral victory for the proposer (Han Brunner) because he succeeded in converting a significant number of the audience to his side during the course of proceedings. Whilst we have not witnessed any hysteria in our ranks concerning the impact of ES/WGS on clinical practice (we are keeping calm), we are speculating furiously on how the brave new world will look, and whether there will be jobs for all until retirement (for many now postponed by a few years). This speculation, combined with genuine concern about the shape of things to come from a commissioning perspective, and the belief that there will be no new money for expansion (unless we can generate new income), suggests we might be heading for a ‘perfect storm’.

Regarding job security, the simple observation of recent history is that each and every quantum leap in genetic technology has led to more work in the clinic, not less. The integration of genetics and genomics in general medicine is necessary and desirable, but realistically only a proportion of trainees and consultants in other specialties will absorb it to the degree that they can do without us, and we should brace ourselves for more work on the clinical interpretation of ES/WGS, exactly as we have been experiencing with array-CGH. To take the view that ES/WGS will ‘solve everything’ to the extent that clinical geneticists will be redundant is to adopt a mainly Mendelian, and determinist and reductionist, view of the genome. We can expect ES/WGS to neatly solve some clinical conundrums, draw a complete blank in others, and elsewhere raise more questions than answers for many patients and families, especially where the phenotypes are indistinct. We will probably be talking more about all those ‘(gn)omes’ that now adorn our vocabulary – the splicosome, the transcriptome, the proteome, the metabolome, the inflammasome and, yes, the phenome.

Everybody agrees that good phenotyping, placed alongside data from ES/WGS, is crucial if any meaningful health gains are to be realised. But it is a far messier exercise than the task of storing massive amounts of genome data and we currently have very poor infrastructure...
There was a gathering, one Friday in September, of some 200 people at Churchill College, Cambridge to celebrate the centenary of the first ever Chair of Genetics. Along with the Arthur Balfour Chair came a substantial residence, which seems to have doubled as office, laboratory and tennis court for the incumbent, on the site of Churchill College. Reginald Punnett (do you remember Punnett squares and 9:3:3:1?) was the first occupier until he retired in 1940. The second, much more illustrious scientist to occupy the Chair was Ronald A Fisher (1943-57), and the third (John Thoday) was still enthroned when I studied for the Part II in 1975. This was the year of Ed Southern's paper in the Journal of Molecular Biology on nucleic acid transfer to nitrocellulose (Southern blotting) which, arguably, ‘began it all’.

Those present all had some past or present connection with the Department of Genetics, which has moved from the suburban garden plot it occupied in my time to a prime site in the university today. Needless to say, the tiny garden shed that was mammalian genetics has given way to much grander facilities, although the fruit fly has not been ousted completely.

Clinical geneticists have always been able to position themselves neatly between genetic technologies (the laboratory) and the clinic (patients). The new technologies will not change this and all the signs are that our contribution is valued, and will be increasingly necessary as our role evolves in the days ahead. As well as our knowledge and skills spanning traditional genetics, genomics, clinical skills, and an ability to counsel, one might also add that we should ‘Keep Calm and Carry On Adapting’.

This is my last contribution to the BSHG Newsletter as President of CGS. I have enjoyed the job to which the CGS membership elected me, despite the pace of involvement constantly accelerating – or so it seems. Jill Clayton-Smith, who needs no introduction, will take over in March and I do urge the membership to support her as I myself have felt supported.

References
Trainee column

Hannah Titheradge, Birmingham

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For those planning to take this examination in March 2013, there are a number of practice questions on the Royal College of Pathologists’ website. The syllabus and candidate information can also be found here. For those trainees in the UK, there are also a number of practice questions on the yahoo SpR group website. Dr Alex Murray, Consultant Clinical Geneticist in Cardiff, has also kindly organised a study day on 1 March 2013, which I would encourage you to attend.

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Congratulations to Meena who has now taken up a Consultant post in Sheffield. We are therefore looking for volunteers to take up the second SpR representative post on the CGS council. If anyone is interested or has any questions about this, please feel free to contact us on meena.balasubramanian@sch.nhs.uk or hannah.titheradge@bwhct.nhs.uk. Thank you to Meena for all her hard work.

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those on tumour invasiveness, mutational patterns, small RNA reprogramming of heterochromatin, ES cells) and others were less medical but nonetheless of great intrinsic interest (establishing the axes of development in the Drosophila embryo, the population structure of Britain). The two talks that I most enjoyed were those of Edith Heard (now in Paris) on the study of nuclear compartments and X chromosome inactivation, and the talk by Ottoline Leyser on plant hormones and the essence of being a plant. I remembered auxin and gibberelin from school days but my knowledge of plant hormones stopped there. There is much more to know than that. Whereas animals develop, then grow and then behave, plants continue full speed at both growth and development throughout their lives; so we animals may be thought of as having behaviour as a substitute for continued growth and development. Which strategy would you prefer to adopt, if you had the choice?

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Genetics on Twitter – a beginner’s guide

Shane McKee, Belfast

There is no doubt that Twitter (http://www.twitter.com) can be an enormous waste of time, and for people who don’t use it on their PC (blocked by most Trusts) or smartphone, it can be puzzling, and perhaps a little distressing to see otherwise sensible people spending their quality time on inconsequential instagrams of cafe products, cats and other junk. However, if used selectively and dynamically, it can be a very useful tool for keeping up to date and interacting with people in near-real time.

Twitter is a database of short messages uploaded by users, and available to the world. You normally only get to see tweets that correspond to your filter settings, so you’re not inundated by every tweet posted by every person ever (that can only be a good thing). Messages (“tweets”) are limited to 140 characters. This forces you to be concise, but you can include URLs, which are automatically shortened. Photographs can be tweeted - use with caution.

Users are identified by an @ character at the start of their username, mine is @shanemuk (please don’t follow me – it’s not worth it). If your username is mentioned in someone’s tweet, Twitter will notify you.

A timeline is a chronological list of tweets from people you follow (you tell twitter that you want to view their tweets, and up they pop). In general if you’re following more than about 100 active tweeters, that’s too many. People do not need your permission to follow you, and that asymmetry is useful. It means you can ‘unfollow’ someone without any nagging guilt. Oh, and never follow anyone who describes themselves in their little biography as a ‘social media expert’, because now you know they aren’t.

Bioinformaticians and some medical journalists have been ‘live-tweeting’ conferences for a couple of years now, using the ‘hashtag’ (#) facility. The recent American Society of Human Genetics conference was tweeted extensively using #ashg2012 – if you click on this hashtag within a tweet, it will pull up all other tweets on the topic.

Clinicians in the UK are a bit slow off the mark on this. I tried tweeting some of the proceedings of the March Clinical Genetics Society meeting under #cgs2012, but with very little response. Either it’s an outright failure, or everyone who was interested in the proceedings was actually there. It is of course very bad form to tweet unpublished research findings without explicit permission, and patient photographs or confidential information should never be tweeted. Twitter is open to anyone with an internet connection.

Many people tweet interesting news items or short comments on newly published papers. There are even Twitter journal clubs. It pays to be careful, however, because what interests the ‘twittersphere’ (“twitterome”? ) is highly filtered and processed by brains that get obsessively agitated about inconsequential minutiae.

If you follow some of the big celebrities, you will notice that they throw questions out into the ether, get millions of replies, then wax lyrical about how wonderful twitter is for answering questions. Well, yes it is. For them. In reality, little people like us never get answers to our questions, and if your question is important, you should speak to a real human or take things through more reliable channels. You should of course never ever reveal information about real patients.

People frequently post their personal opinions and rambling rants on pretty much anything, which means that you’re bound to take offence at something. It pays to develop a thick skin, and to think before you tweet. Many people who tweet things you are interested in will also tweet inane rubbish. If it particularly bothers you, simply unfollow the individual.

It is possible that some of your patients may end up following you. This is often difficult to spot and difficult to stop. Simply be aware that it may happen, and make sure you are happy you can maintain appropriate professional boundaries, as in ‘real life’. The GMC recently carried out a consultation into the use of social media by doctors, and are about to issue further updates to their existing guidance on the topic.

Communication in the Internet Age is shifting rapidly, and it would be unwise to regard Twitter as Social Media’s apotheosis. However, if you do find ways of making this crazy unregulated medium work for you, please do share. Many societies and organisations are using Twitter to communicate with their members. Prominent journals and news outlets are pushing more and more content out via social media. This is going to work for some people and not for others. If it’s not your thing, move swiftly along, but at least keep an open mind and keep thinking.

Further information
Some thoughts relating to the GMC advice on doctors’ use of Social Media:
I find the following accounts interesting to follow. Listing them is not an endorsement.

@PatientsFirstUK – standing up for the interests of patients in the NHS
@RareDiseaseUK – representing rare genetic disorders
@Unique_charity – Unique, dealing with rare chromosomal problems
And of course @ladygaga for comment on the latest developments in high throughput sequencing, bioinformatics and the developmental biology underpinning medically significant human characteristics.

http://www.gmc-uk.org/guidance/10900.asp

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@GeneticsSociety – American Society of Human Genetics.
@dgmacarthur – Dan Macarthur, high throughput genomics and direct-to-consumer comment
@leonidkruglyak – Leonid Kruglyak, Genomics and evolutionary biology
@genomesunzipped – an occasional blog from various luminaries in the next generation sequencing world
@timspector – Tim Spector, genetics educator, twinning and epigenetics researcher
@AdamRutherford – Adam Rutherford, TV science presenter with a genetics slant
@HansRosling – Hans Rosling, statistics guru and surprise TV hit
@BBCnews – general news headlines
@NatureNews – Nature magazine
@BioNewsUK – news and ethical commentary from the frontiers of medicine @ThePapersBehind –primary references for some of those shock-horror research stories that hit the news
@SciencesVital – defending scientific understanding and funding in the UK
@SenseAboutScience – promoting scientific literacy in UK society

Deadline for contributions for next issue is 30 April 2013

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Editorial

As we go to press, the first flakes of snow have exposed the weaknesses in our transport infrastructure (was it the wrong kind of snow again?), while the enduring recession and rising energy prices nudge us to put on another layer of clothing rather than whack up the thermostat. We have some excellent articles in this issue and I am indebted to Phil Dean and Sarah Burton-Jones for reminding us that there is more to attending scientific conferences than simply taking along a poster; they are about learning and they are about networking! Yes, you can actually see, in the flesh, those people whose names you are so familiar with from your reading, and – who knows – you might be bold enough to talk to them and discover that they are as interested in your work as you are in theirs! Making those connections is so important in one’s work – whether diagnostic or research – and major collaborations can begin with a brief encounter in the bar!

Also in this issue, Thalia Antoniadi’s piece on SNPs and SNP checking makes for interesting reading. Although we have visited this subject before, Thalia’s emphasis on an evidence-based approach is most welcome. After all, SNPs are not going to go away, and rather than subscribing to the dogma of ‘another SNP – another primer’ labs should at least have some knowledge of the risk assessment. Good work Thalia, but I suspect it will warrant another visit in a year or two!

Tom Cullup’s contribution is a nice précis of a paper currently in press and, although it looks a bit like one of those ‘rare disease – rare gene’ papers, it does demonstrate the synthesis of different lab techniques in the identification of a gene. A nice example to use in your FRCPath exam, methinks! And on the subject of FRCPath, thanks to Gail and Gareth for the examiners’ feedback on last year’s Part 1 exam; an encouraging pass rate, too. Commiserations to those who didn’t make it. Do try again!

Finally, Mohammed Ghanim provides an account of the Breast Cancer Screening Service in Iraq and shows the value of international collaboration in such areas.

In other news, a report by Sarah Boseley in the Guardian (5th December 2012) suggests that the NHS is not ready for the introduction of whole exome sequencing, or, as the proponents put it, “to reap the benefits of this technology”. Well, there’s a surprise! Don’t be disturbed if you feel a sense of déjà vu here, as you immediately think of other technologies (stem cells, sex selection, etc etc) whose development has outstripped the snail’s pace of ethics committees and others. Boseley’s research is not brilliant (the obligatory shot of a DNA sequence is still the good old autorad!) although she does manage to include a mention of 23andMe, but without the expected conclusion that this technology is not safe in the hands of commercial enterprises who already have a dodgy track record of ‘personal lifestyle’ genetic testing.

Perhaps the most telling quote in the piece comes from Sir Mark Walport, director of the Wellcome Trust, who says: “I was always taught at medical school that you should never do a test unless you could do something with the results”.

This editor hopes you had a very merry Christmas and wishes you all and a peaceful New Year!

Martin Schwarz

For the information of CMGS members: In the ACC section there is an article outlining the structure of the Association for Clinical Genetic Science (ACGS). This article also contains important information regarding nominations for committee members.
Allelic drop out due to PCR primer binding site SNPs: A CMGS Survey

Thalia Antoniadi, David Baty and Sian Ellard (with thanks to all CMGS members who contributed data)

Introduction

The presence of a Single Nucleotide Polymorphism (SNP) within a primer binding site can cause non-amplification of one allele during PCR. For a diagnostic test this can have serious consequences if it leads to a false negative result due to drop out of the mutant allele. During mutation scanning this would result in a missed diagnosis, but in the context of a predictive test allelic drop out can lead to an incorrectly reassuring result. If the primer binding site SNP is on the normal allele then an apparently homozygous mutation would be observed. In most scenarios this would be identified as an unexpected result and is less likely to result in a diagnostic error.

Today it is common practice to check PCR primers for SNPs during the design process, each time a new build of dbSNP is released and/or when performing predictive tests. The SNPcheck tool developed by the NGRL in Manchester has proven invaluable for the diagnostic community, with the ability to search data from the latest build of dbSNP and the 1000 Genomes project. But as the number of identified SNPs now exceeds 38 million (dbSNP 137), it can be very difficult to design primers that bind to sites free of SNPs.

The level of risk of incorrect results due to PCR primer binding site SNPs is not known. Based on the rarity of examples where allelic drop out is known to have caused an apparently homozygous mutation it is likely to be very low. However, given the consequences of a false negative predictive test, some laboratories routinely use two sets of primers for predictive testing.

The aims of this survey were:

1. To collate examples of proven allelic dropout and investigate the location of these SNPs within primer binding sites.

![Graphical representation of the location of the SNPs within the primer binding sites.](image)

Figure 1

Graphical representation of the location of the SNPs within the primer binding sites. Each square represents a nucleotide position; direction is shown as 5’ to 3’ for all primers. Primers with one SNP are shown at the top and primers where two or more SNPs were identified on the pair are shown as sets (set 4 includes a SNP within one primer and a deletion within the second).
"Even SNPs close to the 5' end of the primer may cause allelic drop-out"

Methods
Examples of allelic drop out were requested from all CMGS laboratories in May 2010. Laboratories that were using two sets of primers were asked to provide data on the frequency of discordant results.

Results
Five laboratories reported 12 PCR amplicons where allelic drop out had been observed and further testing using alternative primers identified a heterozygous SNP within one of the primer binding sites. Six of the SNPs had been reported on dbSNP. The 12 primer sets were rechecked for SNPs using the SNPCheck3 tool on 7/11/2012 and all except one were found to have one (or more) SNPs within the binding site. The location of the SNPs within the primer binding sites ranged from the penultimate 5' base to the penultimate 3' base (Figure 1) with no evidence of clustering at the 3' end of the primer.

Laboratories were also asked whether they use one or two sets of primers for predictive testing. Five of the 21 laboratories (24%) use two sets of primers. The remaining 16 use one set only.

Five laboratories provided data for testing with two sets of primers. One laboratory had tested 337 cases with two sets; all comparable results were concordant. Another re-tested 80 cases referred for RET/MEN1 predictive testing following the first report of a false negative predictive test result and found no discrepancies. Collectively the Scottish laboratories have identified 10 cases of allelic drop out due to a primer binding site SNP in 10,725 tests performed over an 8 year time period. This equates to a frequency of 0.093%. These cases occurred before routine checking of primers via the NGRL SNPcheck tool was available.

Conclusions
Twelve cases of confirmed allelic drop out due to a SNP within one of the primer binding sites were reported by 5 laboratories. Our limited data set illustrates that the location of a SNP does not correlate to the likelihood of allelic drop out and even SNPs close to the 5' end of the primer may cause allelic drop out.

The data from Scotland suggest that the risk of a false negative predictive test result due to allelic drop out is low (<0.1%) but these data are restricted to a subset of genes/amplicons for which predictive testing is provided. It is reassuring to learn that no additional cases have been identified since the number of known SNPs has increased/the NGRL SNPcheck tool has become available.
I would like to thank the CMGS for their generous travel grant which allowed me to attend the ESHG conference. There was an excited atmosphere when I arrived in Nuremberg - my plane landed just as final time was called in Germany’s Quarter-Final Euro 2012 match against Greece and it felt like the entire city was in the streets celebrating a win. The venue for the ESHG conference was vast, which reflected the large scale of the conference. At any one time there were up to six sessions running in parallel as well as posters and trade stands, so my biggest difficulty over the four days was deciding which presentations to attend!

One of the highlights of the conference was hearing how next generation sequencing (NGS) is being developed for diagnostics across Europe and USA. Marcel Nelen from the Veltman Group at Nijmegen Medical Center, Netherlands, described their experiences of diagnostic exome sequencing for heterogeneous diseases. Although they sequence the whole exome they initially look at a “gene package” of up to 200 genes for one of five disorders- blindness, deafness, movement disorders, oncogenetics and oxidative phosphorylation diseases. If this proves negative they can go onto explore the whole exome, where they have established a set procedure for dealing with incidental findings. When patients consent for testing they must agree that “all medically relevant findings, including possible findings not related to the initial enquiry” will be reported. An independent panel which includes a clinician, an ethicist, a legal representative and a scientist meets to review incidental findings to decide whether they should be reported. The Dutch group are also using trio sequencing (parents and affected child) to detect de novo mutations for learning difficulties and reported a high detection rate (~25%) in a cohort of 100 trios tested.

I presented my MSC Healthcare Scientist training project, testing for familial hypercholesterolemia using NGS, at a well-attended ESHG satellite meeting sponsored by Agilent. I also had the opportunity to discuss the challenges of providing a diagnostic service using NGS with colleagues already experienced in providing this. This included members of other CMGS laboratories also presenting at the ESHG: the Leeds Molecular Genetics Laboratory now having sequenced over 1400 patients and the Manchester Laboratory have a well-established retinal dystrophy panel. NGS quality aspects were a hot topic through the conference and Chris Mattocks from NGRL, Salisbury, discussed some of the key aspects to consider when validating tests. This includes the number of samples required to validate an assay with as many as 300 unique variants being required to show a sensitivity ≥99% (95%CI). Also an important consideration is the read depth required to detect heterozygous variation with a given accuracy; theoretical estimates can be made using a binomial distribution, although the actual level required for a confident call is technique and mutation-type dependent.

Throughout the conference there were several interesting workshops and discussion sessions including ones on cascade screening: relatives’ right (not) to know, the ethics of biobanking and the procedures for dealing with NGS variants. There was also a strong research element at the conference with several speakers using NGS for research. A group from University of Utah School of Medicine, Salt Lake City, USA, used exome and whole genome sequencing to investigate the rate of de novo SNV mutations. Interestingly they found there was a bias of 5x more de novo mutations occurring through a male parent of origin than through the female germline. Most SNVs appeared to occur at random locations, however approximately 7% occurred in clusters, but the mechanism is unknown.
Ghent Elastin Meeting 2012

Sarah Burton-Jones, Clinical Scientist, Bristol Genetics Laboratory, Southmead Hospital BS10 5NB UK

This September I was very fortunate to be able to attend the 7th European Elastin Meeting in the beautiful city of Ghent, Belgium, thanks to generous funding from a CMGS travel award.

The conference took place in the 13th century Het Pand building, originally a monastery, now part of the University of Ghent and a true blend of ancient surroundings and modern facilities, not to mention the home of an elegant restaurant where we enjoyed an excellent conference dinner. Speakers had to compete for attention with the stunning stonework of the ceiling in the lecture hall, but we were grateful for the thick stone walls keeping the interior cool while outside Ghent experienced a heat wave.

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The ELN gene encodes tropoelastin (the subunit of elastin). Sporadic or autosomal dominant Supravalvular aortic stenosis (SVAS, MIM #185500, incidence approximately 1 in 20000) and the rare condition Autosomal Dominant Cutis Laxa (MIM #123700) are associated with mutations in the ELN gene. For background to my own work setting up screening of ELN I had read many papers on the subject, and it was exciting to find that many of the well-published authors in the field were at this meeting. I was able to put faces to the already familiar names and it was a pleasure and a relief to have some of my queries about elastin resolved by face-to-face discussion with the experts. For a small, specialist meeting (just over 100 participants) there were many impressive results and images displayed, and it is surprisingly difficult to select just a few highlights to mention.

The renowned Professor Lynn Sakai (Shriners Hospital, Portland) opened the conference with a captivating journey through microfibril medicine, looking at disease-associated aspects and the molecular interactions of fibrillins.

Tropoelastin was introduced by Tony Weiss (University of Sydney) as a ‘molecular nanospring’; its coiled domain has the potential to stretch up to 8-fold without rupture or energy loss and then return to its original state (though in vivo this stretching is limited by cross-linking). An animation of the molecule demonstrating its hypothesised scissor and twist movement and multimer assembly was fascinating, as was his description of the different domains and their involvement in tethering, flexing and binding other matrix proteins. Elaine Davis (McGill University, Montreal) shared striking images of the disruption of elastin structure in the aortic wall in knockout mouse models of specific genes. Others discussed the effects of elastin depletion on blood pressure, arterial stiffness and hernia risk. Marie-Paul Jacob’s work (Paris Diderot University) implicated a role of calcium and potassium channels in the control of elastin synthesis.

This was primarily a research meeting and I must admit I have never seen so many photographs of unfortunate mice and zebrafish in such a short space of time; I carry a lasting image in my mind of a mouse aorta! However, it was an unusual opportunity and a privilege to hear first hand how the studies of animal models and in silico work translate into advancement in clinical diagnostics, elucidating molecular pathways and leading to targeted therapies.
Mutations in EPG5 cause Vici Syndrome, a multisystem disorder with defective autophagy.

Thomas Cullup, DNA Laboratory, GSTS Pathology, Guy’s and St. Thomas’ NHS Foundation Trust

Vici syndrome [OMIM 242840] is a rare multisystem disorder characterized by callosal agenesis, cataracts, cardiomyopathy, combined immunodeficiency and hypopigmentation (figure 1).

Various eminent speakers presented clinical perspectives on syndromes including Marfan, Williams-Beuren, dominant and recessive Cutis Laxas, Arterial Tortuosity, Pseudoxanthoma Elasticum, and other still rarer conditions, with discussion of pathogenic mechanisms. Professor Bart Loeys gave a succinct presentation of his recent work on TGFβ2 and mutations in this gene which cause a distinct phenotype within the Loeys-Dietz Syndrome spectrum of disease (published in Nature Genetics in July 2012).

In an engaging talk Sharon Terry, president and CEO of Genetic Alliance reminded us all of the power and importance of lateral thinking and co-operation amongst the whole community of interested parties in genetics. This might have appeared out-of-place on the programme, but turned out to be one of those talks that perhaps we all need to hear.

I set out for Ghent wondering how 3 and-a-half days could be filled with the subject of elastic fibres, and came away feeling it was a shame that it was all over just as I was getting into it! Without doubt I learned a great deal about elastin and its neighbouring components in the elastic fibre complex, and this gave me additional confidence and enthusiasm as we launched a new UKGTN service for ELN mutation analysis at Bristol Genetics Laboratory.
Exome Sequencing was the best way to uncover the causative gene

Following library construction and enrichment using the Agilent 38Mb all-exon SureSelect kit, we sequenced each patient on one lane of an Illumina GAIIx (76 base-pair, paired-end reads), hosted by the NIHR GSTFT/KCL Biomedical Research Centre. In common with most other molecular diagnostic laboratories we do not have in-house bioinformatic expertise and therefore have purchased NextGene for analysis of our next generation sequencing applications. However, through our links with the KCL biomedical research centre, we were also able to run the analysis in parallel through the exome analysis pipeline on the KCL computing cluster. We employed similar strategies for identifying the causative variants in both the NextGene and KCL datasets. Namely, following removal of known variants and synonymous changes, we looked for homozygous variants which were shared by the two patients from the consanguineous kindred. Nine genes from the NextGene dataset and eleven genes from the KCL pipeline showed shared homozygous novel variants. Interestingly, only five variants were common between the two analyses; differences are likely to be accountable by alternative mutation calling algorithms, false positive calls in one or other dataset and differences in the queried databases of known variants. To minimise risk of missing causative variants we looked for mutations in all genes from both analyses in the remaining two exomes. We quickly identified a single gene, **EPG5**, in which all patients had homozygous or compound heterozygous mutations. All were truncating or affect the canonical splice recognition sites. The **EPG5** mutations were present in both the NextGene and KCL datasets. We confirmed the **EPG5** mutations in these patients by Sanger sequencing and have subsequently identified mutations, mostly truncating, in 12 additional families, including the parents of the patient first described by Carlo Dionisi-Vici.3

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"Autophagy is implicated in a wide range of pathologies"

neurodegeneration, aging and heart disease; some of the features of Vici Syndrome are explicable from these relationships, but others potentially demonstrate novel functionality. Previous associations between autophagic defect and Mendelian disease include Danon disease [OMIM 300257], X-linked myopathy with excessive autophagy (MEAX) [310440] and Infantile-onset autophagic vacuolar myopathy [OMIM 609500].

Through collaboration with Prof. Mathias Gautel's group at the Randall Division of Cell and Molecular Biophysics, King's College London, we were able to show that Vici Syndrome patients indeed have defective autophagy. Consistent with the findings of Tian et al\(^4\) we showed a derailment of autophagosomal clearance, a late stage in autophagy, in Vici Syndrome patients, although the precise function of EPG5 in this process is not yet known.

We hope to pursue further characterisation of the autophagy pathway and related genetic conditions. We offer diagnostic testing of EPG5 for patients with Vici Syndrome.

This work is in press for publication in Nature Genetics:

Cullup T et al, Recessive mutations in EPG5 cause Vici syndrome, a multisystem disorder with defective autophagy.


4 Tian, Y et al C elegans screen identifies autophagy genes specific to multicellular organisms Cell 141, 1042-55 (2010)
Iraqi Familial Breast Cancer Strategy

The Service Setting

Cyril Chapman 1, Mohammed Ghanim 2
1. West Midland Regional Genetics Service and Pathology Laboratories (UK) Director
2. National Center for Early Detection of Cancer /Genetic Test Unit

In Iraq, about 45 new cases of breast cancer were diagnosed per 100 000 population in 2008 and about 40% of these cases aged below 50 which is the target age group for familial breast cancer study.1

The demand for genetic services for women with a family history of breast cancer in Iraq has increased exponentially over the last few years. The classification of risk into ‘at population’, ‘moderate’, and ‘high risk’ depending upon the assessed lifetime risk of breast cancer, allows for the appropriate management and early detection programme to be set up for each risk group.

Elements of Iraqi Familial Breast Cancer Strategy:

In Iraq, for the first time, a new strategy of familial breast cancer management has been developed at the National Center for Early Detection of Cancer/Genetic Test Unit based on NICE guidelines and specifically on the West Midland Regional Genetics Service/Birmingham with some modifications that seems to be compatible with the Iraqi health system and Iraqi society as outlined in figure 1.

Referral criteria:

We have used NICE guidelines as a cornerstone in the Iraqi Familial Breast Cancer Strategy and specially the West Midlands Regional Genetics Service/Birmingham as a reference for the referral criteria which are as follow:

- Breast Cancer below the age of 40
- 1 close relative, age under 40
- 1 close relative with bilateral disease
- 1 male relative, any age
- 2 close relatives, age under 60
- 3 affected close relatives, any age

Risk Assessment:
The BRCA2PRO, 2,3,4 Myriad II,5 Couch (also known as Penn),6 Family History Assessment Tool (FHAT), Manchester,7 IBIS,8 and Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)9 models have all been developed to estimate the risk and predict the probability of identifying germline BRCA mutations in an individual or a family.

![Figure 1: The main elements of the familial breast cancer strategy (FHF= family history form)](image-url)
In Iraq, we have depended on IBIS, BOADICEA and Manchester score. We have used CaGene software and we are trying to get the widely used software in UK, Clinical Pedigree software which is the modern version of Cyrillic software as it facilitates the use of many of these models with a highly professional level of pedigree drawing.

**Genetic Testing:**
A small proportion of the familial breast cancer cases are fit for testing and this depends solely on the results of the risk assessment study and the geneticist’s opinion.

<table>
<thead>
<tr>
<th>RISK GROUP</th>
<th>10 YR RISK</th>
<th>SCREENING</th>
<th>AGE AND FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>&lt;3%</td>
<td>Mammography</td>
<td>50-70 3 yrl &gt;70 on request</td>
</tr>
<tr>
<td>Moderate</td>
<td>3-8%</td>
<td>Mammography</td>
<td>40-50 Annual 50 + as population</td>
</tr>
<tr>
<td>High</td>
<td>8-20%</td>
<td>Mammography</td>
<td>40-50 Annual 50 + as population</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt;8% (30-40) &gt;20% (40-50)</td>
<td>MRI &amp;Mammo. Mammography only</td>
<td>30-5- Annual 50-75 18 monthly then as local program</td>
</tr>
</tbody>
</table>

Table 1: The breast guidelines used in the strategy and its relevant screening (adopted from WMRGS /Birmingham – UK with permission)

Manchester score\(^7\) recommends testing in those who have a score which exceeds 15 (which is the cutoff for the 10% threshold) for BRCA1/BRCA2 testing.

Currently, we are testing the candidate patients as a first step targeting the founder mutations which are 185 delAG, 188 del-11 bp, 5382 InsC in BRCA1 and 6174 delT in BRCA2 and as a second step we will test the gene by MLPA BRCA1/2 sequencing.

**Acknowledgement:**
Special thanks to the Minister of Health Dr. Majeed H. Ameen, Dr Sabah Aldeen, Andrew Cuthbert, Prof. Nada Nathir and best regards to all people supporting the work of the unit in UK/Birmingham and Baghdad.

**References:**
Feedback on the FRCPath Part 1 written examination 2012

Gail Norbury, Guy’s & St Thomas’ NHS Foundation Trust, London and Gareth Cross, University Hospital NHS Trust, Nottingham

There were a record number of 23 candidates for the Part 1 FRCPath written examination held on 20 March 2012. Sixteen candidates (70%) were successful with a number very close to passing. We hope these candidates feel encouraged to re-sit.

As in previous years, the main problem in performance was with exam technique; not addressing the specific question but just writing on the topic or only addressing one part of the question and omitting some basic core detail. Some candidates prepared good plans but then did not appear to use them for the essay. Poor technique also applied to the short notes. Paper two was in general slightly less well answered than paper one, reflecting the general weakness in applying rather than recalling knowledge. Candidates are thus encouraged to start practising both essay and short notes under examination conditions much earlier in their preparation schedule and to reflect further on the purpose of the question before starting to write. Candidates are required to answer four out of five questions on each paper and need to score over 47% on each paper.

PAPER ONE

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

This question was common to both the molecular and cytogenetic papers. It was a popular question, attempted by 19/23 candidates and reasonably well answered with 74% passing and the highest average score. The question was designed to include not only gene therapy exon skipping, and compounds used to allow read through of stop codons but other areas such as substrate limitation, enzyme replacement, removal toxic metabolites, stem cell therapy.

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

This question was also common to both the molecular and cytogenetic papers. Again it was a popular question with 19/23 candidates attempting but with only 47% passing. A key area of weakness was in not addressing the question but just writing about the technique of next generation sequencing with little reference to specific and different issues relevant to application for prenatal diagnosis such as the enhanced detection rates in specific referral groups, reporting time/gestation time, sample requirement, follow-up studies, targeted and whole genome analysis, work-flow, education and training requirements, resource requirements, clinical utility. A number of candidates focussed almost entirely on next generation sequencing with only scant consideration of aCGH.

3. Describe advances in therapy for genetic disorders. Include examples of at least 3 different strategies

This was the least popular question, with 10/23 attempts but was reasonably well answered with 60% passing and the question with the second highest mean score. The question was designed to include not only gene therapy exon skipping, and compounds used to allow read through of stop codons but other areas such as substrate limitation, enzyme replacement, removal toxic metabolites, stem cell therapy.

4. Describe the molecular pathology underlying Lynch syndrome and how this may be used to devise a diagnostic testing strategy

A popular question, answered by 22/23 candidates but with only 50% passing. The general weakness was in just writing about Lynch syndrome, not describing the hallmark features such as microsatellite instability, how MSI leads to cancer development, failing to discuss how these features can be used to derive an efficient testing algorithm with reference to sample requirements, and to help distinguish between familial and sporadic cancers.

5. Write short notes on the molecular pathology and inheritance of FOUR of the following:
   a) Fragile X
   b) Retinoblastoma
   c) Achondroplasia
   d) Leber’s hereditary optic neuropathy
   e) Hereditary neuropathy with liability to pressure palsy

This was attempted by 22/23 candidates with 50% passing. The main weakness was in failing to mention such basic issues as the pattern of inheritance, range of mutations, penetrance, variable expressivity, genetic heterogeneity. Some sections were unnecessarily long and some very brief suggesting candidates needed to give more consideration to time allocation. Leber’s hereditary optic neuropathy was the least popular option.

PAPER TWO

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

This was a question common to both the molecular and cytogenetic papers. It was answered by 20/23 candidates of which 65% passed. Some answers were very narrow and many did not consider both the benefits and challenges. Issues raised about practical implementation were often very shallow and did not expand on what specific aspects of training or competence needed to be addressed.
2. Describe the operational issues to be considered in the adoption and implementation of non-invasive prenatal diagnosis using cell free nucleic acid
Answered by 18/23 candidates of whom 50% passed. The key weakness was in not addressing the operational issues in sufficient detail and instead focusing on the pathophysiology. More information was expected about the care pathway, use of test for screening or testing, service delivery, education of users, quality assurance.

3. Describe the principles of the Analytical validity, Clinical validity, Clinical utility and Ethical, legal & social implications (ACCE) Framework for test evaluation in the context of genetic services
This was a reasonably popular question, answered by 17/23 candidates but had the lowest number of passes at 35% and the lowest mean mark. Whilst candidates were able to provide some definition of the terms, there was a general weakness in relating these dimensions to the purpose(s) of the test within a clinical service. Most candidates also failed to define sensitivity and specificity. Many candidates failed to consider the feasibility of test delivery and acceptability of the tests to the patients.

4. Compare and contrast the principle features of existing and emerging sequencing technologies focussing on those relevant to clinical diagnostic application
This was the least popular on paper two, attempted by 16/23 candidates with a 50% pass rate. The main weakness was that many candidates failed to include capillary Sanger sequencing as an existing technology and just described the different 2nd and 3rd generation chemistries. There were a few very good answers where the candidates had addressed the question including key practical consideration for service use such as validation, higher sensitivity for detection of acquired mutations, the use of gene panels to increase mutation detection sensitivity, interpretation and service delivery

5. Describe FOUR of the following and the relevance to human disease, clinical diagnostic testing or gene identification
a) Non-sense mediated RNA decay
b) X-inactivation
c) Epigenetic modification
d) Genome Wide Association studies (GWAS)
e) Heteroplasmy
This was the most popular question on paper two, answered by 21/23 candidates with the highest pass rate of 71%. Genome Wide Association studies was the least popular option. Heteroplasmy was generally the best and epigenetic modification the least well answered individual option. Candidates needed to address both parts of the question and demonstrate a clear understanding of the particular phenomena and its significance to diagnostics. For epigenetic modification, a suitable definition would be changes in gene expression that do not involve changes in DNA sequence. Suitable examples to illustrate the relevance to diagnostics would include MLH1pm hypermethylation in sporadic colorectal cancer with MSI, X-inactivation and manifesting females, imprinting and Angelman syndrome. For each of these the appropriate means of analysis and inclusion in testing algorithm should be included. A common reason for loss of marks was lack of sufficient detail. For example, a frequent problem with part a) was a failure to explain clearly the tendency for NMD to not occur for nonsense codons in the last exon or 50 nucleotides upstream from the last splice site. A frequent problem with part b) was to not explain that X-inactivation occurs in early embryogenesis and passed on thereafter from cell to cell. A description of the mechanism (with the role of XIST) was provided in the best answers. In d) the best answers not only described how GWAS was carried out, and the role in complex disease research, but also described the lack of clinical usefulness for most diseases, and the role of the common-disease-common variant hypothesis
Editorial

Welcome to the latest edition of the Cancer Genetics Group Newsletter and a very belated happy New Year!

At last year’s CGG spring conference in Newcastle we were delighted to be joined by a strong contingent of clinical geneticists from the Netherlands including several members of our sister organisation, the Dutch Cancer Genetics Group (DCGG). We thought it would be interesting to ask one them to give us an insight into their group’s activities. DCGG group chair, Frederik Hes, kindly accepted up our invitation. Fred, Wendy van Zelst-Stams and Fred Menko offer a fascinating overview of the DCCG, including its origins in 1998, their educational activity and an expanding research portfolio, which includes several strong Anglo-Dutch collaborations. He’s also sent us a photo of their team.

In October last year the PHG Foundation hosted the latest in a series of workshops for the Collaborative Oncological Genetics-Environment Study (COGS), a major EU funded multicentre project. The study is investigating the potential for exploiting genotypic and environmental/lifestyle information to improve individual cancer risk prediction and intervention strategies such as breast screening. Susmita Chowdhury at the PHG Foundation in Cambridge has kindly written a briefing for CGG News covering some of the key elements of the project, such as integration and implications for public health and also ethical, legal and social issues.

As you know, moves are afoot the update and much improve the BSHG website. The CGG section is also due a revamp. Julian Adlard continues to make a huge contribution to this major undertaking and has very kindly written a progress report.

Most of us will be familiar with Cancer Research UK’s Stratified Medicine Programme (SMP), arguably a major step towards personalised therapies for people with cancer in the UK. The programme was launched in 2011. Now, with the end of phase one approaching, Helen Stuart at the All Wales Molecular Genetics Service, Cardiff (one of the three Technology Hubs) offers a timely summary of the excellent progress made so far. Helen also highlights some of the many challenges ahead for the SMP and the benefits it potentially could offer to the NHS and its patients.

In the last issue we spotlighted cancer genetics services in Wales. In this edition, our series of perspectives on regional cancer genetics services moves to Leicester. Julian Barwell offers a fascinating snapshot of the myriad initiatives his team are developing to address the complex challenges to providing an effective, penetrating service for this corner of the East Midlands.

We finish with a very special and fascinating retrospective from Professor Shirley Hodgson on her long and illustrious career in clinical genetics. We are all hugely indebted to Shirley for the immeasurable contribution she has made to cancer genetics through her clinical and academic work. I think the title of her marvellous Cook’s tour says it all!

Andrew Cuthbert, CGG News Editor
A word from the Dutch Cancer Genetics Group

Frederik Hes, chairman
Wendy van Zelst-Stams, secretary
Fred Menko, member and coordinator of the DCGG guidelines committee

In the Netherlands we have 120 clinical geneticists, 70 genetic consultants (nurses) and 70 residents. Yearly, about 30,000 individuals seek advice at the nine clinical genetics centres. These numbers have been steadily growing each year by 5-10%. Approximately 30-40% of genetic consultations concern hereditary tumours, of which breast and colon cancer are the most frequent. In cancer genetics, all DNA tests (diagnostic and predictive) are undertaken in conjunction with the clinical genetics centres as we feel that it requires expertise to correctly interpret and communicate a molecular genetic test result.

On 18 December 1998, the Dutch counterpart of the UK Cancer Genetics Group (CGG) was founded. We name ourselves WKO, which could be translated as the working group for clinical oncogenetics. Now, we have been thinking about a more international name as the Dutch Oncogenetics Group, DOG. However, some of our members were not very much appealed by the idea of going to the dogs. But we are happy to say that this is certainly not the case for the Dutch Cancer Genetics Group (DCGG), as we are very much active on three front lines: clinical guidelines; research; and education.

Guidelines

The DCGG has four meetings a year with representatives of all nine clinical genetics departments. With a usual number of 20-30 participants, mainly clinical geneticists, we discuss guidelines for the management and surveillance of families with cancer. In these meetings, the floor is open for case discussions, which leads to suggestions for diagnosis or further management. In this regard, the DOG regularly chases a CAT (critical appraisal of a topic) like ‘should we perform RAD51C or CHEK2 diagnostics in breast and ovarian cancer families?’

We contribute to guidelines on three levels:

1. Evidence-based guidelines in collaboration with the Dutch Association of Medical Specialists. This can either be multidisciplinary guidelines, i.e. breast cancer (www.oncoline.nl) or specific clinical genetics guidelines, i.e. actively informing family members after defining a hereditary cancer syndrome in an index patient.

2. Evidence or consensus-based guidelines for the Dutch society of clinical genetics. These guidelines are multidisciplinary, and are presented in a blue booklet and at www.oncoline.nl in co-operation with the Netherlands Foundation for the Detection of Hereditary Tumours (NFDHT). This booklet contains guidelines for diagnostics and prevention for the 25 most common hereditary tumour syndromes.

3. Specific practical consensus-based (problem orientated) guidelines within the DCGG:
   - Speed procedure for BRCA-genes: consequences for treatment of breast cancer?
   - Desmoid tumours: always colonoscopy and DNA diagnostics?
   - Phaeochromocytoma or kidney cancer: which clinical surveillance and DNA test?
   - Paediatric tumours (solid, brain, neuroblastoma, Wilms): when referral for clinical genetic centres?
   - Polyposis/multiple colorectal adenomas (APC/MUTYH negative): surveillance for first degree relatives

Furthermore, representatives of the DCGG participate in national working groups, e.g. on Lynch syndrome, paraganglioma, Hereditary Breast Ovarian cancer (HEBON), leiomyomatosis and von Hippel-Lindau disease.
Research
Research was not the first purpose for founding the DCGG, but nowadays it progressively fills the agenda of our meetings. Good examples are the two studies that were initiated from the UK, IMPACT and CAPP3, for which we are happy to make a Dutch contribution. The IMPACT study, led by Ros Eeles is a targeted prostate cancer study, which rapidly filled up with 550 male BRCA1 and BRCA2 carriers from the Netherlands. We hope to be successful in the CAPP3 study, as in CAPP2, and supply many Dutch MMR gene mutation carriers to John Burns’ initiative of a dose finding aspirin study in Lynch syndrome.

Within the Netherlands, we co-operate on studies like MIPA (MSI-testing-Indicated-by-a-Pathologist), genotype-phenotype correlations in germline mutation carriers of the EPCAM and PMS2 genes, and for Cowden and Birt-Hogg-Dubé syndromes. Moreover, we participate in research projects via the patient registries of the NFDHT, which are either initiated by Hans Vasen or DCGG members.

Education
Every two years we fill in the educational program for all Dutch genetic counsellors. Last time we had as our main theme ‘what is under the skin’. Here we presented the rarer tumour syndromes with skin manifestations such as Carney complex, Cowden syndrome and Peutz-Jeghers syndrome. After the lunch break we woke everybody up with a short quiz to test their knowledge. We ended the day by presentations of ‘knowns and unknowns’ with at least two presentations per centre and preferably presented by clinical geneticists in training.

Yearly, we participate in the training of residents of internal medicine. We educate them on hereditary tumour syndromes, principally on the more common ones such as breast and colon cancer and also show them tools to recognize patterns in detecting the more rare forms of hereditary cancer.

Last, but not least, we have our highly-valued meetings of the UK and Dutch CGGs. These joint meetings started in 2007 in Manchester. Subsequently, we had a venue in the Artis Zoo of Amsterdam and we had an excellent meeting in the Life centre of Newcastle this year. In 2014 we hope to welcome you all at a spring meeting in Leiden!

CGG Webpages

This short note is to update you regarding the changes to the CGG section of the BSHG website, and to invite suggestions for new content. CGG has owned the domain name ukcgg.org for a number of years, which most members will have accessed indirectly after first entering the BSHG website. BSHG have recently commissioned a new website, in which each of the constituent and associate groups, including CGG, have been allocated separate areas.

The new website uses a web content management system, which allows addition and modification of pages, within certain constraints, whilst maintaining the overall design. This improves our ability to directly edit the content. There is also the potential to make some areas more secure by making them available only after a login.

As a result of these changes, we will be putting the ukcgg.org domain name into mothballs, and managing our future content through the new BSHG website. CGG members can enter through the BSHG website, and will be able to directly bookmark the specific CGG pages as usual.

It is fair to say that the CGG webpages have contained only limited information previously. At the time of writing, this includes links to details of the winter meeting, some other conferences and courses, and the application details for Travel Awards. We are keen to improve the information available for members and will be putting additional content there, for example constitution, steering committee information, news items, and links to guidelines and research studies. We would also welcome suggestions for additions or changes to the contents which can be emailed to me (julian.adlard@leedsth.nhs.uk) or any other Steering Group member.
Collaborative Oncological Gene-environment Study: a briefing from PHG Foundation

Susmita Chowdhury, PHG Foundation Cambridge

What are the public health implications of adding new knowledge about genetic information to the health risk equation? What are the challenges for service delivery systems and the health information landscape? What about the cost-effectiveness, benefit and harm of including genetic testing in prevention programmes? And how do we prepare for the ethical and social consequences of introducing targeted prevention programmes?

The PHG Foundation in Cambridge, a public health organisation with 15 years’ experience of considering the potential of genetics within public health programmes, is working with researchers from the University of Cambridge to investigate some of these questions. The Cambridge group are collaborators in a multicentre European Union 7th Framework Programme (FP7) funded research initiative, COGS (Collaborative Oncological Gene-environment Study, www.cogseu.org). The overall goal of the COGS project is to use genotypic and environmental/lifestyle knowledge of the 200,000 participants of their collaborative consortia of 200 groups to improve individual risk prediction and intervention strategies.

As part of this work, the PHG Foundation used modelling to show that it was possible to use polygenic risk information along with other factors such as age to stratify a population into different risk groups that would receive different preventive interventions. Taking breast cancer as an example, the model suggests that offering mammographic screening to women between 35 and 79 years of age based on their polygenic risk profile and age would result in a 24% reduction in the numbers of women being screened for only a 2% drop in cancers detected (personal communication, Pashayan 2012). The model indicates that introducing targeted breast cancer screening could enable the detection of almost as many cancer cases as the present age-stratified system, but would involve screening fewer women. This may help to avoid the adverse effects of screening, such as, a reduced number of false positive cases and over-diagnoses, as well as being potentially more cost-effective.

As the above example shows, targeted screening for breast cancer using genotyping may extend the opportunity to benefit a wider age group than those currently screened and result in a more optimal benefit–harm ratio for the programme as a whole. However, implementation of such a screening programme raises a number of issues in addition to effectiveness and cost effectiveness, such as the acceptability and practicality of introducing genotyping into the screening encounter. In addition to undertaking economic modelling work, the PHG Foundation team held a series of expert stakeholder workshops to discuss the organisational, ethical, legal and social issues that might arise with the introduction of risk-stratified screening of the population for breast/ovarian and prostate cancer.

These workshops explored how a targeted screening programme could be put into practice. As one of the experts in the multidisciplinary workshops commented about the introduction of more fine-grained risk stratification into pre-existing screening programmes “this is when it starts to get difficult”. The workshops highlighted several issues concerning implementation if targeted screening is to be seriously considered. First, implementation needs to be tailored to the national or regional context and should proceed on an incremental basis, for example implementation should involve the modification of established screening programmes rather than the wholesale introduction of new processes/systems. Second, management of individuals should be informed by evidence of the balance of benefits and harms in the risk category they belong to. Individuals must be fully informed of the benefits, harms and uncertainties of a risk-assessment and subsequent screening. Third, the storage and access of genetic data must be safeguarded from use by third parties such as employers and insurers. Fourth, to ensure efficient management health professionals may need further training about the role of common genetic variants in disease susceptibility and receive support in using risk-stratified screening in their health practice. Finally, there is a need for empirical studies that assess the benefit-harm balance, ethnic generalizability of particular risk variants and the public acceptability of targeting screening on the basis of genetic as well as environmental data.

In the final phase of the COGS project, the PHG Foundation is working on a comprehensive report that will outline the implications of risk-stratified screening for breast and prostate cancer along with policy recommendations for implementing this type of personalised cancer preventive strategy in the general population.
Cancer Research UK Stratified Medicine Programme: what we’ve achieved and where we’re heading - the Cardiff view

Helen Stuart, All Wales Molecular Genetics Service, Cardiff

Background
Phase 1 of the two year Cancer Research UK Stratified Medicine Programme (CRUK SMP) started in September 2011. The programme aims to collect and genotype 9000 tumour samples over two years for a range of genetic markers specific to each of the six tumour types. The two major aims of the programme are:

1. To develop a model within the NHS for the consent, recruitment and genetic analysis of patient samples, all within clinically relevant timescales.
2. To correlate patient clinical and outcome data with genetic markers, as a future resource for translational research and development.

Progress to date
The three selected Technology Hubs (Cardiff All Wales Regional Genetics Laboratory, West Midlands Regional Genetics Laboratory and Molecular Diagnostics Laboratory at the Institute of Cancer Research) and eight Clinical Hubs (Cambridge, Edinburgh, Glasgow, Leeds, the Institute of Cancer Research, Cardiff, Manchester and Birmingham) have worked tirelessly over the course of the programme to successfully recruit and analyse approximately 4000 patient samples (Figure one). Taking into account the large number of patients consented in October, the programme is on course to achieve its 9000 patient target by June 2013.

Sequence change data
Each patient tumour sample is analysed for a tumour-specific set of genes at one of the three Technology Hubs. The gene panels include some genes for which NHS diagnostic tests already exist, e.g. KRAS and EGFR, because specific mutations in these genes are already known to relate to patient treatment outcomes. Other genes in the panel have been chosen because they have implications in tumourigenesis and may be important in future stratification of cancer patients, for example BRAF, TP53, PTEN.

Data on mutation frequencies has been shared between all technology hubs (Figure two). Initial analysis of the data indicated great consistency in mutation detection between each of the technology sites for the majority of clinically related genes, namely BRAF, KRAS, NRAS, PIK3CA and EGFR. Variation was shown between the pick-up rate of sequence changes in TP53 and PTEN as also in the TMPRSS-ERG fusion gene. This could be attributed to differences in the sensitivities of the techniques used at each lab (Sanger sequencing versus CE-SSCA), as well as the effect of macro-dissection on sequence change detection. This is only performed in two of the labs. However, differences in the dataset collected by each of the hubs have been identified. Therefore no definitive conclusions can be drawn at this time and more work is currently being done to provide a more rigorous analysis of the data.

The sequence change data along with a large clinical data set on cancer treatment and response is collected for each SMP patient. During the course of year two, analysis of this data set will be performed to try to highlight areas of interest, for example co-existence of sequence changes within a particular tumour type, or links between a certain change and patient outcome. All of this data will then

Figure one: CRUK SMP patient recruitment and testing progress
“Interest in the SMP has been great, the programme has already been expanded”

Figure two: Comparison of sequence change detection rates in year 1. Purple = Molecular Diagnostics Laboratory, Institute of Cancer Research. Maroon = Cardiff All Wales Regional Genetics Laboratory. Yellow = West Midlands Regional Genetics Laboratory.

be available to researchers through a central data repository at the Eastern Cancer Registry and Information Centre (ECRIC) and may be useful to future research projects.

Quality measures
Consistency in reporting between Technology Hubs and interpretation of results are two of the issues that are regularly discussed at meetings between laboratory staff and CRUK colleagues. These issues are paramount in order that the data from all three Hubs can be collated with ease at the end of the SMP.

The implementation of a National External Quality Assessment Service (NEQAS) scheme in July 2012 has helped to ensure standardisation across the Technology Hubs. This scheme will consist of three EQA rounds with each round assessing the testing of samples from all six tumour types. The style of NEQAS scheme being followed is different from existing schemes in that each NEQAS tumour sample is analysed for a group of tumour-specific genes rather than a single gene. The first EQA round yielded excellent results for the programme with all Hubs scoring 97.9% and above. Round two of the scheme is currently underway.

Informatics
The implementation of a universal electronic request and reporting system at all of the Technology and Clinical Hubs has been a huge achievement of the programme. Pseudonymised patient data is routinely transferred between the Clinical Hub where the sample is collected and the Technology Hub, which performs the appropriate analysis and reports the results via a File Transfer Process server. Although potentially costly and time-consuming in implementation, the adoption of this paperless system by the NHS could reap rewards in the future and would be a long overdue step forward into the 21st century.

Turnaround times
The target turnaround time for the full range of gene test results to be available to Clinical Hubs is 15 working days. This has proven to be a challenging target in light of the testing methods currently used by the Technology Hubs and the large screening-based analyses required for some of the genes. This target was, however, met for >90% of lung, melanoma, colorectal and breast samples reported by the Institute of Cancer Research in October. Therefore, it is certainly achievable but highly dependent on workload and test methods used.

Expansion of panel testing
Interest in the SMP has been great and the programme has already been expanded in terms of the addition of BRAF gene analysis in February 2012 across all tumour types. This change was led by Roche in order to collect data regarding the frequency of BRAF V600 activating mutations in non-melanoma patients. It has already been shown that metastatic melanoma patients with BRAF V600 mutations have improved survival when treated with vemurafenib. Therefore, would non-melanoma patients with BRAF V600 mutations also benefit from this drug?
“These developments show the huge potential for the data set”

In September 2012, the SMP lung panel was expanded as part of a partnership project with Bristol Meyers Squibb to include BRAF exon 11 and 15 sequencing for all SMP lung samples and DDR2 gene sequencing for all squamous lung samples. These developments show the huge potential of the data set that will be generated by the SMP and the importance of the banked tumour and blood DNAs to the research community.

Future
Owing to the turnaround time pressures, the Technology Hubs are moving towards gene panel testing utilising Next Generation Sequencing (NGS). The use of NGS will streamline testing processes and could show how such a service could be delivered at clinically relevant turnaround times for the NHS. However, in order to make NGS feasible for the SMP the process must be optimised for poor quality fragmented tumour samples. Consideration must also be given to other more general NGS issues of ensuring full and even gene coverage and interpretation of variants.

To date the CRUK SMP has proven to be:

- Challenging in terms of the informatics requirements of the programme
- Beneficial in terms of working collaboratively with the other Technology Hubs
- Useful in forging new relationships with our clinical colleagues across the UK
- Rewarding, particularly now that mutation data is beginning to be evaluated

The CRUK SMP continues to be a great project to be involved in and we at All Wales Molecular Genetics Service are privileged to have been part of this initiative. We hope to maintain our working relationship with CRUK in future projects and look forward to exciting developments within the field of stratified medicine.

References
The Leicester Cancer Genetics Service

Julian Barwell, Leicester

We have been developing a familial cancer genetics clinic in Leicester over the past five years. We have been able to obtain funding for MRI breast screening, germline and tumour block testing for HNPCC, a moderate family history of breast cancer clinical service and Comprehensive Clinical Research Network consultant and nurse sessions. Specialised mendelian clinics are due to start in the spring.

Referrals for inherited cancer and tumour detection rate have increased more than five fold. We have increased clinic room capacity four-fold and we are delighted that Dr Joyce Solomons has recently joined the team, alongside the cancer genetic counsellors (Demetra Georgiou, Penny Van Besouw and Catherine Hartigan).

We have been working with Dr Jacqui Shaw in the University of Leicester and Professor Charles Coombes at Imperial in an attempt to develop an array-based somatic genetic signature in plasma for women at risk of, and affected with, inherited breast cancer. We have been very kindly supported by a HOPE Against Cancer and a Cancer Research UK programme grant and hope that these tests will help compliment both germline testing and computer modelling of risk in order to improve risk assessment and decision making for women considering preventative surgery and chemotherapy.

Alongside this we are studying the inheritance of non-alcoholic fatty liver disease, been continuing our research into radiation induced heart disease in breast cancer patients, and developing a novel technique to identify gene fusions in the urine of men with high grade prostate cancer.

Genetics education outreach has been traditionally strong in Leicester based largely on the discovery of DNA fingerprinting by Professor Alec Jeffreys. We have major concerns about rising rates of cancer and diabetes in ethnic minorities in Leicester. The ‘Tipping Points’ project undertaken by Leicester cancer genetics services in collaboration with Genetic Alliance UK showed that individuals with a significant family history of cancers from black and minority ethnic groups (BME) are more likely to be referred later to cancer genetics services, with marked differences in the reason for referrals in comparison to non-BME groups. With genetic outreach road shows and the use of community champions, referrals from BME groups have now greatly increased.

In partnership with Macmillan, the National Institute for Health Research and De Montford University, we have developed a counselling concept called ‘wrap-round care’ involving: a palliative care outreach service; psychotherapeutics; genetic counselling (led by Mrs Vanita Jivanji); clinical psychology and the use of surgical patient buddies; the first clinical genetics YouTube channel; and close links with community stakeholders. This counselling umbrella concept supports the ‘medical supermarket’ whereby cancer patients and their relatives are placed at the centre of access to survivorship services including: geneticists; dieticians; physiotherapists; researchers; the chemoprevention team; the smoking cessation team; Macmillan Cancer Support; local support groups; and the wrap-round care team encouraging communication between patients, clinicians and researchers.

A bid has been submitted to the ‘Big Society’ at the Department of Health for each genetics centre in the country to be able to establish a similar Clinician, Community and Academia Research Engagement (C-CARE) with the National Hereditary Breast Cancer Helpline.

By working alongside academic, hospital and community partners, we aim to identify high risk families and use the medical supermarket model to support survivorship and the cascading of information to at risk relatives.
If I Were You I Wouldn’t Start From Here

Shirley Hodgson, St Georges, London

My career has been based on serendipity; I trained as a GP (having done house jobs in paediatrics and obstetrics on the advice of the careers advisory service, who said that women were best off being GPs, and this training was appropriate), and I only entered genetics after I was sacked from an evangelical GP practice for prescribing “the pill” to unmarried women, when I took up a locum post in clinical genetics at Guy’s, with Professor Polani, Caroline Berry and Chris Garrett. I found this so absorbing, exciting and fulfilling that I gave up my long-held avoidance of genetics (for hereditary reasons!), and decided to become a clinical geneticist. Of course there were hurdles; I had not previously thought it necessary to do the membership exam, so I had to take a house-job in paediatrics in order to equip myself for this. It was difficult with two small children to care for, but thanks to fantastic support from my husband I managed, and returned to Guy’s in a substantive registrar post.

I did my MD on Duchenne Muscular Dystrophy, partly at the Hammersmith Hospital with Professor Dubowitz, and the DMD gene was identified during that time. I remember being so amazed by the fact that different mutations in the same gene could cause such different disease severity, with the realisation later that in-frame deletions could cause mild disease, whereas out of frame deletions were clearly very deleterious. This was all very new and exciting.

I stayed at Guy’s when Professor Bobrow came, but then took up a consultant clinical genetics post at Addenbrooke’s in 1985. I became interested in cancer genetics when I was there. I knew that Vicky Murday and Joan Slack were running a pioneering “Cancer Family Clinic” which Joan had set up in 1986, because of the work done by Richard Houlston and Vicky using Lovett’s data on patients seen with colorectal cancer (CRC) at St. Mark’s Hospital in London. This showed that the risk to relatives of a case of CRC of developing the condition themselves was directly related to the number of affected relatives in the close family, and their age at diagnosis. Joan was much derided by some colleagues for this at the time, but audits of the outcomes of this clinic, which arranged colonoscopic surveillance for those with a family history conferring 1/10 risk of CRC during their lifetime, bore out their expectations, and showed that early cancers could be detected and treated in this way. At this time the characterisation of “Lynch syndrome” by Patrick and Henry Lynch, with studies of the outcome of colonoscopic surveillance for at-risk individuals in these families, had raised awareness of this condition, and Joan was arranging surveillance for individuals in such families, with gynaecological evaluation for the women.

It was at about this time that my husband (a gastroenterologist) was looking after a charming lady with CRC who had also previously had endometrial cancer. As it turned out, she was the mother of my cousin’s wife. I remember becoming very concerned because it seemed to me that she could have Lynch syndrome, and after overcoming my initial reticence about approaching my cousin, I phoned her, and she agreed to see Joan Slack. Screening was arranged, but sadly not straight away because she was pregnant, and subsequently she developed… and died from….ovarian cancer. The strange thing was that the extensive family history of CRC had not previously been appreciated by the family. This was clearly a very emotional experience for me and caused me to think hard about how we could raise awareness of cancer genetics. Serendipitously, Eamonn Maher and I (both in Cambridge at the time) were approached by Cambridge University Press about publishing a book on some aspect of clinical genetics, so we decided to write a book on cancer genetics, and this saw the birth of ‘A Practical Guide to Human Cancer Genetics’.

Before 1990 there were virtually no cancer genetics referrals to clinical genetics departments, and of course now these comprise almost half of referrals. Bruce Ponder did some clinics at the Royal Marsden Hospital and Guy’s, and there were clinics starting at Manchester, Oxford and Newcastle. When I returned to a consultant post at Guy’s in 1990 I set up the cancer genetics clinic serving the South East Thames Region; there was a steep learning curve developing these clinics and their remit.

The paradigm for genetic registers for conditions predisposing to cancer were those for Familial Adenomatous Polyposis at St. Mark’s and in other countries, notably Canada, Denmark and the Netherlands, who showed clearly that following up and screening at-risk relatives greatly reduced morbidity and mortality from cancer. Subsequently registers were set up for other cancer predisposing conditions. I tried to obtain funding for such registers, but it was difficult to decide who should be responsible for monitoring and arranging surveillance for individuals at risk in such families, and the appropriate pot of funds to finance this, as the NHS said it was research, and the research bodies said it was service! I did a survey of the opinions of GPs, geneticists, gastro-intestinal surgeons and gastroenterologists, and everyone said it was someone else’s responsibility to monitor these families!

Whilst at St. Georges, Rosalind Eeles and I obtained funding from Macmillan Cancer Care for a comparative study of two methods of delivering cancer genetics...
“I remember spending a long evening in the bedroom at the home of this family, taking blood from all the family members that we could get hold of.”

services: the implementation of nurse-led clinics in several general practices and two district general hospitals (co-ordinated at St George's Hospital), and a system of telephone clinics (co-ordinated at the Royal Marsden Hospital). This also addressed the question as to whether there should be active ascertainment of ethnic minorities, since they form a very low proportion of individuals referred to cancer genetics clinics.

I initiated a multidisciplinary clinic for families with VHL at Guy's in the 1990s, and set up a similar clinic at St. George's when I moved there to a Chair in Cancer Genetics in 2003.

In 1990 Joan had just retired, and Professor Walter Bodmer asked if I would like to take her place running the Family Cancer Clinic at St. Mark's, and I agreed. He also helped me to obtain Imperial Cancer Research Fund (ICRF) grant funding for translational research into cancer genetics. I became involved in the Cancer Genetics Group, initiated around 1990 as a discussion forum for research into aspects of clinical cancer genetics, and this raised awareness of clinical cancer genetics practice.

In the 1990s I became a member of a European BIOMED project headed by Neva Haites, which examined many aspects of breast cancer genetics, and we had a marvellous time investigating various aspects of this; my particular role was to do a survey of cancer genetics services in Europe. Interestingly the extent and development of such services was strongly related to whether nurses and genetic counsellors were allowed to participate in delivering such services. This project led to further international collaborations which I have very much enjoyed, and I became a long-lasting member of the Public and Professional Policy Committee of the European Society of Human Genetics, and a member of the international ‘Mallorca Group’, which meets regularly to develop collaborative research into hereditary colorectal cancer, and guidelines for management of predisposed individuals.

With ICRF funding I have mentored a series of nurse-counsellors and research fellows, each of whom developed their own specific lines of research. We pursued studies on p53 staining in tumours in relation to apoptotic response to DNA damage in lymphocytes (Sheila Mohammed), looked for germline missense mutations and rare allelic variants in the ATM gene in early-onset breast cancer (Louise Izatt, with Ellen Solomon), worked on the identification of the role of FANC gene mutations in leukaemia, and in breast cancer susceptibility (Marc Tischkowitz, with Chris Mathew), and followed several lines of investigation including lymphocyte radiosensitivity in BRCA1 and BRCA2 mutation carriers, and implications for breast cancer susceptibility (Julian Barwell). It was gratifying to see how the research contributed to the professional progression of these research fellows.

Sadly our Prevention Of Endometrial Tumours study, investigating the possibility that the Mirena intrauterine device could be a useful prophylactic option for women with Lynch syndrome, folded for lack of recruits within the time frame allowed (partly because of the year-long process we needed in order to obtain all the ethics and other accreditations needed for a multi-centre trial) - the premature death of a poet! I have been very involved in collaborative research over the years, particularly with Ian Tomlinson (ICRF-Cancer Research UK), initially at St. Mark’s, predicated on the huge patient resource there. One particular coup was when Nick Wright asked me if I could identify a patient with FAP who had a mosaic cell line. I was able to do this, a male mosaic “Turner syndrome”, and an important paper, the “Polyclonal origin of colonic adenomas in an XO/XY patient with FAP” was published in Science as a result of this serendipitous finding. Other studies at that time included the identification of a large Jewish family with hereditary mixed polyposis syndrome. I remember spending a long evening in the bedroom at the home of members of this family with Stewart Whitelaw, taking blood from all the family members that we could get hold of, whilst they had a party downstairs with all the many relatives they had invited on our behalf. I don’t remember either of us eating or drinking any of the delicious spread that evening, as we were too busy! The causative gene has only just been identified! More recently Andrew Beggs has been an active researcher working jointly with me and Ian on various aspects of CRC, including studies on whole genome methylation in adenomas and carcinomas, finding that ‘GRASP’, which encodes the general receptor for phosphoinositides-1 associated scaffold protein, was differentially methylated in CRC, and studies of loss of expression of DSB repair proteins and survival in colorectal cancer.

I have a great interest in international medicine and teaching, and currently run a BSc module at St. George’s in cancer genetics. I am embarking on several conferences in India on this topic in January 2013, as part of my interest in promoting the subject internationally. I am now also very involved in teaching the medical students in the new University of Namibia Medical School, and my husband and I are going to Windhoek regularly for a month at a time to help develop the new curriculum there.

What fun it has been… and still is!
Date for your diary

Julian Adlard

The CGG Spring Meeting will be held at The Queens Hotel, Leeds on Wednesday 22nd May 2013. This will be a single day meeting. The Queens Hotel is situated a very short walking distance from Leeds Railway Station. There are several car parks close by and a direct shuttle bus runs from the Airport. We expect to invite abstracts in early 2013. Programme details will be updated on the CGG website. Please keep this date free in your diary. We look forward to seeing you there.

CGG News Editor

Deadline for contributions for next issue is 30 April 2013

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Editorial

Public health genomics is an advancing, dynamic field; producing significant and innovative findings applicable to fundamental population health matters. In this issue we are treated to insights into the exciting work currently conducted at the Institute for Public Health Genomics (IPHG) at Maastricht University in The Netherlands and their collaborators across Europe.

I am delighted to introduce the articles for this issue of the SGPPH’s contribution to the BSHG newsletter. Our featured articles submitted by researchers at IPHG will share with you the advances in public health genomics in Europe. Professor Angela Brand gives an impeccable introduction to public health genomics, from her perspective as founding Director of the IPHG, in our lead article and the activities of the Public Health Genomics European Network (PHGEN) in our second article.

In our third article Elena Ambrosino discusses the exciting work of The Genome-based Research and Population Health International (GRAPH-Int) Network. Our final articles address some of the significant practical applications of the IPHG’s work in population health which include application in Chlamydia diagnostics, smoking cessation and the development of the Learning-Adapting-Leveling model which assesses the feasibility of developing technology for uptake by healthcare systems and policy.

I do hope you enjoy reading this issue as much as I have had in collaborating with Professor Brand and preparing it. I’d like to thank each of our authors for their excellent articles delivered in very tight deadlines and particularly Professor Brand for all her hard work and enthusiasm in co-coordinating the process. I would also like to encourage all of you interested in hearing more about Professor Brand and her team’s work to get in touch with her at the email address provided in her lead article.

Our next issues will focus on cancer genomics from a public health genetics perspective. For all those working in this area and interested in writing for us, please be in touch. I wish you all a prosperous 2013 and look forward to bringing you our next issue.

Dr Angelique Mavrodaris
Public Health Genomics – from cell to society

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Truly personalised healthcare drives a fundamental change not just in what is known, but also in how we think of ourselves and the way we are living, thus redefining our society. We have to prepare for all the various organisational changes ahead of us. The real paradigm shift depends on the willingness to restructure our current policies. So far, all stakeholders including policy-makers and the private sector are struggling to translate the emerging knowledge into public health. Public Health Genomics (PHG) is the area of public health ensuring that scientific advances in genomics (“from cell…”) triggered by innovative technologies are timely, effectively and responsibly translated into health policies and practice for the benefit of population health (“…to society”).

New insights are being obtained from genomics, proteomics, transcriptomics, metabolomics, epigenomics, microbiomics, and other ‘omics technologies. As these data are integrated through the use of information and communication technologies (ICT), we are at the edge of achieving an understanding of the systems biology and systems biomedicine of human health and disease that also incorporates environmental contributions such as life-style, toxic agents, social and economic factors as well as health systems determinants. These developments and the involvement of the patient brought forward the concept of P4 (predictive, preventive, personalised and participatory) medicine serving already as a blueprint for Public Health Genomics to prepare healthcare systems and policy makers for this shift in our approach to healthcare. P4 medicine is no longer a vision - it’s a mission. We need to go beyond the P4 medicine and recognise in the light of a “systems approach to public health”, that:

- Common complex diseases can be considered in terms of a constellation of “rare” diseases, each of which reflects a complex biological system
- We are moving away from a traditional classification of disease and towards groups of shared pathology that can be described as “diseaseomes” or disease nodes
- We are moving away from a focus on risk factors within biostatistical models of populations and towards an emphasis of individual pathways or networks
- It is time to emphasis personal rather than clinical utility

Until now we still see just incremental progress and changes leading to personalised (stratified) medicine and precision medicine. There is nothing new here. However, combined genomic and phenotypic analysis has become possible thanks to the increasing role of ICT in healthcare driven by improved technological options and the interoperability of various technologies. The complexity of the task when applied to diagnosis and therapy demands algorithms and mathematical models to reduce uncertainties. As a result, efforts are now being made to generate computational models of individual persons (“virtual twins”). Such models can be used to follow individuals throughout their lifetime and enable health professionals to virtually simulate and optimise treatments as well as all kinds of interventions. By following individuals rather than remaining tied to a given healthcare system, it will enable citizens to handle and access personal health-related data whenever needed. IT Future of Medicine (ITFoM) provides such a platform for Europe being one of six pilot projects in the European Future and Emerging Technologies Flagship scheme. It is a very ambitious project, which aims to harness the vast potential of ICT to revolutionize human healthcare and targets to ‘lead the way towards truly personalised healthcare’. Dealing with (in space and time) highly dynamic personal (health) information, moving from the understanding of statistical risks within groups to individualised evidence, and using virtual individual models as a tool is a radical new vision of healthcare!

Health systems across Europe and beyond must prepare for change arriving from such novel ICT solutions in order to reach progress in treating complex diseases. To drive this change it has become clear that the future of healthcare depends upon major breakthroughs in science and technology as well as to translate these breakthroughs in a timely, effective and efficient manner. At the moment there are no models or tools that facilitate the timely implementation of health innovations into the healthcare systems. Tools that are currently available either support the industry side or the health policy side, which means there is a lack of tools that combine both ‘worlds’ and form a bridge between industry and health policy-related stakeholders. The LAL model (Learning Adapting Leveling) has been recently developed and is being piloted. It covers the whole process from the first idea of a product to its implementation in the healthcare system. This will not only help to reduce the gap in the integration timeframe of health innovations, it will also help to come to an early strategic decision on the ongoing
We have to get prepared in time, and we have to define today what kind of guidelines we need for tomorrow.

References:


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The Public Health Genomics European Network (PHGEN)

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Genomics is a highly dynamic field and, as such, represents a moving target for public health. Public health is shifting from a focus on the population towards an emphasis of the individual as a means of supporting the wellbeing of the population. In particular, we are entering the era of predictive, personalised, preemptive and participatory (P4) medicine supported by advanced technological infrastructure. These changes represent a paradigm shift in our approach to healthcare and will go hand in hand with a major reclassification of disease. The challenge now is to understand how all of these changes will impact public health and how to ensure that they are translated effectively into benefits for individual citizens and society as a whole. Thus, there is a need to develop guidelines aiming not to close doors. Instead, the goal is to create a vision that allows for flexibility and adaptability in their implementation in order to have a maximum impact on health, the health care infrastructure, health technologies and economic growth in the health sector.

Therefore, the European Commission asked to develop "European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies" to support the Member States (and other relevant stakeholders) to more efficiently and effectively work together at European level in addressing the challenges deriving from emerging genome-based information and technologies and to prepare for the paradigm shift of personalised healthcare in time. The implementation of the concept of public health genomics being the responsible and effective translation of genome-based knowledge and technologies for the benefit of population health requires modifications of public health and health governance systems on all levels.

The Public Health Genomics European Network (PHGEN II) fulfills this task. It is an EU DG SANCO funded and European Agency for Health and Consumers (EAHC) issued project (EU Project No. 20081302, 2009-2012), which produced recently the first edition of "European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies". The guidelines will assist all EU Member States, Applicant and EFTA-EEA countries with evidence-based guidance on the timely and responsible integration of genome-based information and technologies into healthcare systems for the benefit of population health. They build on the extensive work of the Public Health Genomics European Network (PHGEN, www.phgen.eu) being the cornerstone in the development of public health genomics in Europe. Whereas PHGEN I (DG SANCO 2006-2008) identified the need for European best practice guidelines ("mapping exercise"), PHGEN II developed the first edition of these European best practice guidelines using the concept of "genome-based information and technologies" (Bellagio-Model), which PHGEN I established as a scientific benchmark in Europe. In this concept, genome-based information is very holistic and includes not only all ‘omics’ data, but also environmental, socioeconomic, and lifestyle factors as well as information on health systems. The process of the guidelines’ development was in line with international standards and acknowledge the diversity and cultural differences in Europe. Key experts such as public health experts, EU lawyers, human geneticists, ethicists, systems biologists, Health Technology Assessment (HTA) experts, representatives from the private sector and patient groups as well as key policymakers had been involved in PHGEN II.

On the 19th and 20th of April 2012, experts from across the field of public health genomics representing key European and national organisations and institutions from policy-making, academia and private sector as well as the representatives from all EU Member States came together at the final PHGEN II meeting in Rome to discuss the future of public health genomics and to endorse the Declaration of Rome on 19 April 2012, a summary of the "European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies" (Declaration of Rome, www.phgen.eu).

**Genome-based Information and Technologies**

PHGEN II builds on the definitions that were developed and agreed in PHGEN I, such as the glossary on public health genomics and the status of genetic information and genetic testing. The definitions provided by PHGEN II take into account the most recent developments in the fields of genomics, systems biology, and systems medicine, which provide the evidence base for the “European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies”. The terms genome-based information (GBI) and genome-based technologies (GBT) are encompassed by the term genome-based information and technologies (GBIT).
Within these best practice guidelines, translational research considerations are combined with system management under the concept of public health genomics

Rationale for the European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies

The ultimate objective of PHGEN II is to enable informed decisions at the macro, meso and micro levels regarding quality assurance, provision and use of emerging GBIT. The means chosen by PHGEN II to achieve this is the preparation of European best practice guidelines to support this decision-making process now and in the future. However, meta-level guidance is also needed. This meta-level guidance can be achieved by ensuring that the 10 essential public health tasks, as described within the public health wheel or public health trias (assessment, policy development, assurance) can be adequately fulfilled in each jurisdiction on the basis of a common understanding of best practice guidelines for each task (see Figure 1).

Figure 1: Public health trias / public health wheel [IoM, 1988]

Within these best practice guidelines, translational research considerations are combined with system management under the concept of public health genomics.

The next step - Implementation of the 2012 Declaration of Rome in the EU Member States

Since health is not just a value in itself, but also a driver for growth, only a healthy population can achieve its full economic potential. As mentioned in the Europe 2020 agenda “promoting good health is an integral part of the smart and inclusive growth objectives for Europe 2020. Keeping people healthy and active for longer has a positive impact on productivity and competitiveness. Innovation in healthcare helps take up the challenge of sustainability in the sector in the context of demographic change”, and action to reduce inequalities in health is important to achieve “inclusive growth”.

Thus, as the next step a Joint Action (JA) Public Health Genomics and Personalised Healthcare - Implementing the ‘European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies’ in rare diseases and cancer is planned for 2014 being a joint financing of a public body or nongovernmental organisation by the European Community and one or more Member States. The planned JA fully supports and implements the Innovation Partnership Flagship Action of Active and Healthy Ageing. It covers not only Innovation/Genomics and Health in All Policies (HiAP) in the current programme Together for Health (2008-2013). It also highly prepares for and contributes to the new programme Health for Growth (2014-2020) by applying innovative solutions for improving the
quality, efficiency and sustainability of health systems, putting the emphasis on human capital and the exchange of European best practices. As such, the planned JA will help Member States, which are under pressure to strike the right balance between providing universal access to high-quality health services and respecting budgetary constraints, to reduce healthcare costs and substantially improve the quality of care to all citizens now and in the future. The European best practice guidelines developed within PHGEN II and summarised in the Declaration of Rome address many areas of the Health for Growth Programme, such as health technology assessment (HTA), medical devices, clinical trials and medicinal products, and strengthen the link between technological innovation and its effective and responsible uptake and commercialisation.

In conclusion, building on PHGEN I and II, the planned JA for 2014 will help address the transition to personalised healthcare and personal health from the data-integration and modelling perspective points of view in all EU Member States, Applicant and FTA-EEA countries within the upcoming years.
The Genome-based Research and Population Health International (GRAPH-Int) Network

Elena Ambrosino
Institute for Public Health Genomics, Maastricht University, The Netherlands

Advances in genomic research and related sciences have the potential to positively impact population health around the globe, preventing diseases and improving health outcomes. The integration of genome-based information and technologies into public health research, policy and practice is the overall aim of the field of Public Health Genomics (PHG). With this purpose in mind, international key stakeholders in the field of PHG joined forces in 2005 and established the GRaPH-Int (Genome-based Research and Population Health International) Network (www.graphint.org). The launch of GRaPH-Int closely followed the first international PHG experts meeting group that took place in April 2005 in Bellagio (Italy) and gathered specialists in disciplines as diverse as genomics, public health and ethics.

Since 2005, GRaPH-Int stands as an international collaboration and leading voice to promote the goals of PHG at the global level, share resources in the field, and safeguard equitable access to genome-based knowledge worldwide, including in low and middle income countries. GRaPH-Int aims at being not only a Network, but also an Enterprise, undertaking interdisciplinary initiatives that support dialogue, communication, research, valorisation, education and stakeholder engagement. Its distinctive mission is to promote an international collaboration that facilitates the responsible and effective integration of genome-based knowledge and technologies into public policies, programmes, and services for improving population health.

GRaPH-Int’s key feature is the integration of knowledge from a wide range of disciplines, such as genomic science, population sciences and the humanities and social sciences. The Network aims to provide an international forum for dialogue and collaboration by supporting the development of an integrated knowledge base and making links with other relevant networks and organizations such as WHO, CDC, ECDC or PHAC. The main goals of GRaPH-Int are the following:

- To provide an international forum for dialogue and collaboration
- To promote relevant research and valorisation in PHG
- To support the development of an integrated knowledge base
- To promote education and training
- To encourage communication and engagement with the public and other stakeholders
- To inform public policy (policy advice)
- To facilitate push-pull functions between academia, governmental bodies and the private sector

In May 2010, following five years of successful management by the Public Health Agency Canada (PHAC), the administrative hub of GRaPH-Int was transferred to the Institute for Public Health Genomics (IPHG) within Maastricht University (Maastricht, NL) and the Executive Direction to Angela Brand (IPHG, Maastricht University, NL). In the spring of 2012, the Network, supported by the IPHG, hosted the international GRaPH-Int Symposium in Rome (Italy). The meeting consisted of two sessions: one on Evidence in PHG moderated by Muin Khoury (CDC, USA), Chair of the Executive Committee of GRaPH-Int, and the other on PHG in the field of Infectious Diseases moderated by Servaas Morre (IPHG, Maastricht University, NL), Chair of the GRaPH-Int working group on infectious diseases. The Symposia, that featured 11 prominent speakers in the field and more than 50 participants from around the world, terminated with success and revived the global debate and international collaboration in the field of PHG.

The objective is now to keep expanding the areas of activities and collaborations of GRaPH-Int in order to pave the way for the translation of genome-based knowledge and technologies in everyday healthcare and public health practices.

References:
Chlamydia trachomatis infections and subfertility: activities of the EpiGenChlamydia Consortium and the opportunity to translate host pathogen genomic data into public health

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Chlamydia trachomatis (CT) is the most common bacterial sexually transmitted infection (STI) worldwide. An estimated 92 million cases per year worldwide are reported. The infection is often asymptomatic resulting in patients not seeking treatment. Untreated urogenital C. trachomatis may give rise to late complications, including pelvic inflammatory disease (PID), ectopic pregnancy, and tubal pathology. Women who develop late complications suffer considerable morbidity, and socio-economic and emotional burden. Worldwide, 15% of couples trying to conceive suffer from subfertility.1 In women, one of the major causes of female subfertility is tubal pathology and in all of cases C. trachomatis is the single most common cause for infertility.

Detecting evidence of a CT infection using serology is non-invasive, simple and quick to perform.2 As such, chlamydia serology is often used as a first screening test for tubal damage in infertile women, but has a limited sensitivity of 50-60%. The reference standard for diagnosing tubal pathology in subfertile women is laparoscopy. However, laparoscopy has several disadvantages. First, it is an invasive and expensive procedure (on average 3000 Euros including additional costs), and requires general anaesthesia. Furthermore, it holds a 1.5% risk of surgical complications (e.g. bleeding, infection).

The clinical course of chlamydial infections is heterogeneous; transmission, symptoms, clearance, and development of late complications differ significantly per patient. Epidemiological studies have demonstrated a 40% inheritable component for C. trachomatis infections in humans.3 This opens and validates studies to identify which genes are responsible for this 40%. The innate immune system plays a pivotal role in the first recognition of CT and the subsequent immune response and genetic variation in these genes have been linked to the susceptibility to and severity of C. trachomatis infection.4

The aim of the European EpiGenChlamydia Consortium was to structure trans-national research to such a degree that comparative genomics and genetic epidemiology on large numbers of unrelated individuals could be performed to identify genetic markers to be used in patient profiling to provide a more individualised healthcare. (See www.EpigenChlamydia.eu for details of the consortium).5

Currently part of the consortium has obtained new funding inside the EU based on SME (Small-to-Medium-Enterprise) collaborations with Universities. This EuroTransBio grant has as a main goal to develop a diagnostic test on the basis of human genetics and C. trachomatis serology to better assess the presence of C. trachomatis-associated tubal damage in subfertile women in such a way that not only the sensitivity, but also the positive and negative predictive values increase significantly. This consortium ending in the beginning 2015 is in progress of performing large scale (n=10.000) analyses of human genetic variation to identify novel genetic markers that are able to stratify patients with tubal pathology. The identified SNPs in the pathogen recognition receptors (PPRs) genes have already shown to be highly predictive for the development of tubal pathology. However, single SNPs do not provide a high enough predictive value for a diagnostic test. By combining multiple identified and novel SNPs in the PPR genes and genes in linked pathways, and exploiting them as susceptibility markers in a genetic trait, a highly predictive test for tubal pathology based subfertility can potentially be developed. This will be of great help to women who suffer subfertility.

References
How Public Health Genomics could enhance smoking cessation?

Sylviane de Viron1,2, Herman Van Oyen1
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Public Health Genomics (PHG) is “the responsible and effective translation of genome-based knowledge and technologies into public policy and health services for the benefit of population health” as defined during the Bellagio workshop. In the case of smoking cessation, different uses of PHG may be discussed. Here, we proposed three different applications (1) improving global cares of smoking cessation, (2) developing genetic notification of smoking related disease risk and (3) informing the population on the evidence of the genomic risks.

The first and probably one of the most essential uses is taking care of smokers in a global way. This includes the use of genomic factors such as genes influencing nicotine metabolism and the cascade theory of reward. Moreover, all the non-genomic factors such as social factors (e.g. smoking status of the family members), socioeconomic factors (e.g. level of income) or psychological factors (e.g. motivation to quit smoking) are of high importance. Furthermore, some disorders may be linked to smoking by genetic factors. For example, attention deficit disorder with hyperactivity (ADHD) is associated to a reward deficiency syndrome due to a lack of dopamine. Smoking is a well-known factor inducing the release dopamine. Consequently, smoking may be a self-treatment of patients with ADHD. Therefore, treatments of patients with ADHD have to be adapted during smoking cessation.

Another possibility is the genetic notification of smoking related disease risk to enhance smoking cessation. In that case, genomic factors are no more focused on smoking behaviour but on the risk of smoking related diseases due to a potential genetic risk. A recent meta-analysis show that such kind of notification may improve smoking cessation in follow-up up to 6 months (RR=1.55, 95% CI 1.09-2.21)1. Probably a better impact on longer follow-up may be achieved with reminders of the genetic notification and the assessment of the understanding of the notification.

Finally, more comprehensive information of genomic factors influencing smoking behaviour and smoking cessation to the general population is necessary. The current knowledge of the population is really low. Why people are allowed to get information about non-genomic factors influencing smoking and smoking cessation but not genomic factors? A common concern put forward by some is that providing such “fatal” genomic evidence to the population may excuse their behaviour. However, genomic factors as all the other factors are just one component of the path causing smoking.

In conclusion, taking the smoker as a whole without dissociation of genomic and non-genomic factors is of main importance and PHG is an innovative way to improve the success rate in smoking cessation.

References
Addressing the backlog of genome-based technologies in healthcare

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Personalised medicine sets off a new era of healthcare that currently focuses on the individual genetic signature of patients interacting dynamically with other health determinants such as environmental and lifestyle factors to create a more personalised approach at a much earlier stage to healthcare. The core diagnostic/therapeutic segment of the market comprised primarily of drugs, medical devices and diagnostics is expected to reach €26 billion by 2015. Improvements in genome-based technologies are primarily responsible for this staggering growth. The market is pioneered by small to medium enterprises (SMEs) regarded as the true innovator of personalised diagnostics market, highly contributing to benefits for society as stated in Europe’s growth strategy EU 2020. However, both historically and currently we see that the timely uptake and implementation of these relevant SME-based genomics-related applications in real time is negligible. The average time to diffusion in healthcare systems is over 10-20 years even with marketing approval (FDA, CE, etc.). As a result and given the exponential fast pace of technological development, by the time a relevant application is integrated into the healthcare system, it is considered less relevant as a more effective and efficient application becomes available on the market. Subsequently, both businesses and the population (patients in need of new and more accurate clinical diagnostics) are at a disadvantage. This can increase the burden of disease as well as become a development hurdle for companies in the diagnostics market causing significant problems, i.e. product failure connecting to loss of employment, capital and IP.

Based around this bottleneck of healthcare integration the unique Learning-Adapting-Leveling model was developed at Maastricht University. The innovative nature of this model is that for the first time it brings together in parallel two never before connected yet seemingly striking activities. The first being technology transfer, which is used by industry to translate academic knowledge, patents and applied research into marketable products and the second being the public health assessment tools. The latter is used by decision makers to assess technologies on the market for healthcare implementation/acceptance, guidelines and reimbursement. The Learning-Adapting-Leveling model identifies non-synergy between these two different entities as the reason for the bottleneck of technological integration. The model assesses the feasibility of the developing technology from the start to near the end of the technology maturation process for real-time uptake by healthcare systems and policy guidelines, thereby give real-time recommendations to compensate for any

The Learning-Adapting Leveling (LAL) Model. TT is technology transfer, PHAT is the public health assessment Tools, DM are decision makers and PPP denotes public-private partnership. Through these PPPs, the (innovation) network is developed. The value of information constitutes the technology’s relevance to the target population, processing ability of the user and exclusively in terms of intellectual property rights. The public health genomics wheel encompassing the 10 essential tasks as a reference frame constitute 3 domains namely, assurance, policy development and assessment.
Gaps in the process prior to launching the product and to build contact with policy. This model encourages early-on involvement of all stakeholders including doctors, industry, patient groups, investors, insurance companies, HTA professionals, etc. leaning towards a possible cross-talk and public-private partnership. The model also takes into account and assesses the Value of Information and does control analysis of possible gaps defined through the 10 Public Health Tasks defined at the Bellagio meeting. The model has been officially integrated in the best practice guidelines for QA, provision and use of genome-based information and technologies, FP7s and a few SMEs as well as the EU flagship project ICT Future of Medicine (www.itfom.eu).

References


SGPPH News

Deadline for contributions for next issue is 30 April 2013

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Notes
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