BSHG

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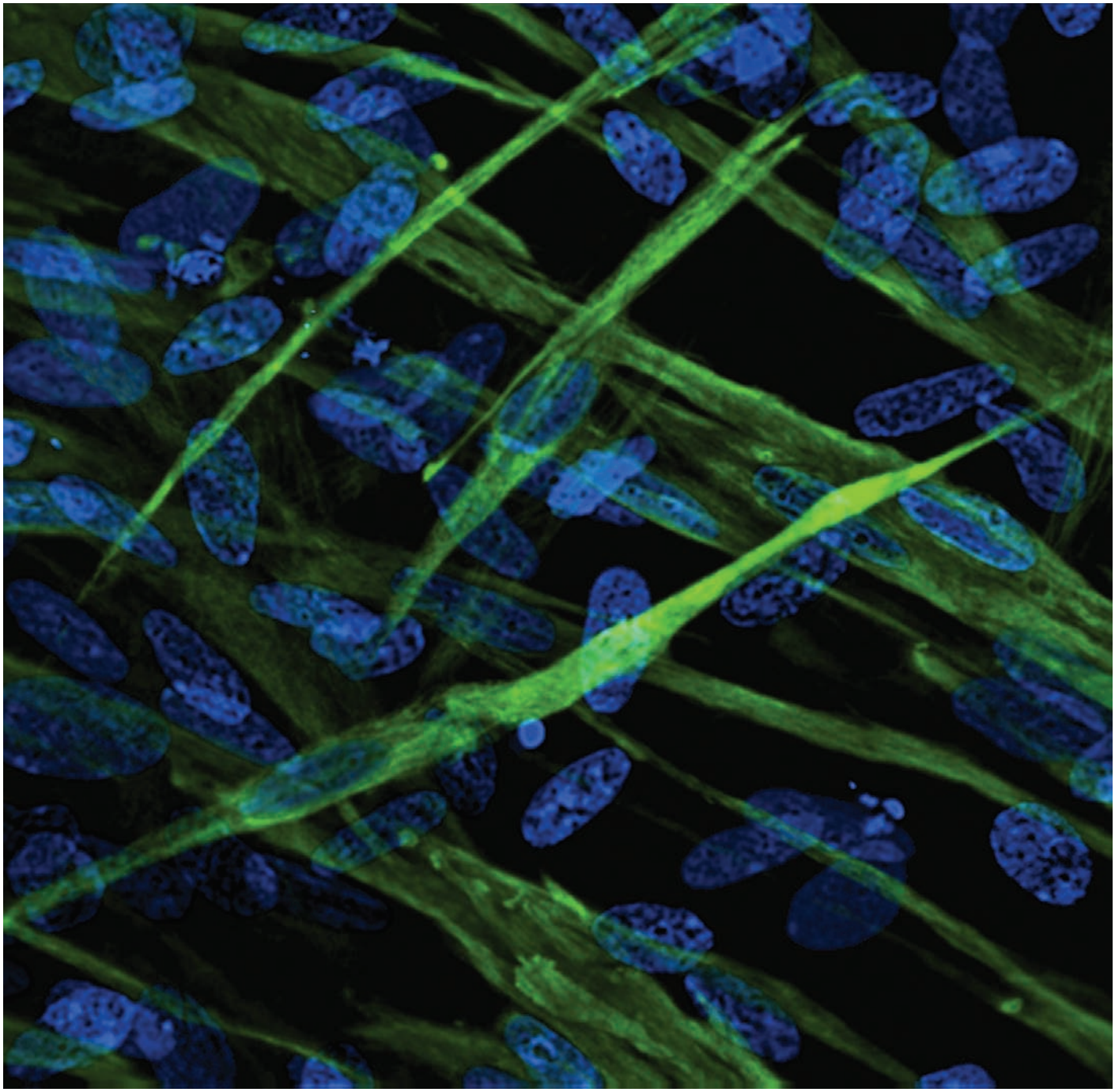
BSHG News



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From the newsletter editor

I am pleased to welcome you to the 42nd issue of the BSHG newsletter. This is the last one you will be receiving by post; from the next issue, BSHG News will be produced electronically. We shall be conducting a survey in the near future; please respond to let us know your preferences for format and content.

In this issue Professor Keith Kerr and Caroline Clark have contributed an article on one of the most promising areas of genetic medicine; the targeting of lung cancer treatments based on tumour molecular pathology; they argue that molecular genetics laboratories have the skills, facilities and quality assurance mechanisms in place to take on this work.

Our new Chair, Chris Patch presents a response from the BSHG to the HGC consultation on DTC genetic testing, and our comments on the government response to the House of Lords enquiry into genomic medicine.

I am especially pleased to introduce the first of a series of occasional articles from individuals who have personal experience of living with a genetic condition; Sarah Winckless is a medal winning Olympic rower, who also has a Huntington's expansion; she gives us some personal insights into her life as a high-achieving Olympic athlete.

I hope you enjoy this issue.

Helen Middleton-Price

From the Chair of the BSHG

Chris Patch

The field of human and clinical genetics is an area of much promise and excitement but also great challenges. These challenges apply to delivering the academic outcomes and gaining a greater understanding of the complexity of human development, health and disease and to the translation and implementation of those outcomes into improvements in the health of individuals and the population.

My question for the BSHG in the short and medium term is how we, as a society, manage these challenges to retain the positive aspects of what we have had but also maintain a central role in the translation and implementation of what has come to be known as genomic medicine.

As those of us who have been around a few years recall, the BSHG was formed as an umbrella society of the four constituent groups that represented the field of medical and clinical genetics at that time. Until then the four individual societies had been functioning independently, and there was no single body for the different professions and disciplines. The first council of the BSHG under the chairmanship of Professor Andrew Read provided the leadership and vision to start the process of developing the BSHG as the Society, representing the interests of all professionals with an interest in human and clinical genetics. Under subsequent chairs the Society has developed the scientific content of its conference and provided a clear steer to the development and expansion of NHS specialist genetic services.

I would suggest that we are now at an interesting point where genetic science will be pervasive across the whole of medicine and healthcare, and the shape of health services is also under pressure to change because of technological advances, devolution, changes in how services are purchased and provided, and, of course, the potential impact of the recession on public spending.

I read with interest the response of the government to the House of Lords enquiry into Genomic Medicine, as this comprehensive report makes many recommendations for the future shape of genomics and healthcare. The challenge for the BSHG is how to respond to all of this in order to ensure that the Society stays relevant and continues to serve, in a positive way, the interests of members.

At the AGM I was delighted that the Society for Genomics Policy and Population Health was accepted as an affiliated group. This builds on the expansion of the BSHG through the Cancer Genetics Group; we have also had approaches from other special interest groups such as Cardiac Genetics. The incorporation of these groups is organisationally complicated but welcome, as I think it broadens the constituency of the BSHG and moves it to a place where it can act as a focus for working in partnership to deliver a strategy for the development and implementation of genomic medicine.

I am privileged to be the chair of the BSHG at this exciting time and look forward to working with the Council and wider membership of the Society, to build on its past success and hopefully provide a steer to its future development.

Lung cancer pharmacogenomics - who, how, where?

Keith Kerr, Professor of Pathology and Caroline Clark, Molecular Geneticist, Aberdeen

Over the last 25 years clinical molecular genetics laboratories have been largely responsible for providing testing for inherited disorders using germline DNA. Some laboratories also undertake somatic testing, for example microsatellite instability (MSI) analysis in colorectal cancer tumours as an indicator of underlying germline mutation in mismatch repair genes.

An increasing knowledge of the molecular pathology of cancers and the related potential to treat patients with specific 'targeted' drugs that exploit particular molecular characteristics of the tumour, will increase demand for somatic testing, driven by the emergence of specific therapies. At present it is unclear who will carry out testing, what methodologies will be used and how this work will be funded.

Epidermal Growth Factor Receptor (EGFR; ErbB-1; HER1) mutation analysis in lung cancer is rapidly becoming accepted as a standard of care in this disease. The results play a pivotal role in selecting patients for treatment with a high probability of success and the demand for this test is rising.

Lung cancer accounts for 22% of all cancer deaths, and is the most frequent cause of cancer death in men and women in the UK. Around 20% of cases are small cell carcinoma; the remaining 80%, often collectively known as non-small cell carcinomas (NSCLC), comprise roughly equal numbers of squamous cell and adenocarcinomas; around 15% of lung cancers are of other uncommon NSCLC subtypes.

The prognosis for patients with this disease is, in general, poor. Around 80% of patients have advanced disease at diagnosis and are unsuitable for potentially curative surgery. In those who are fit enough, the treatment of choice is systemic chemotherapy, but even with treatment, such patients can expect on average to live only 10-12 months from diagnosis.

Patients with NSCLC show variable responses to chemotherapy, and much research is ongoing to develop predictors of response to cytotoxic and other drugs. The most 'mature' of the targeted drugs in lung cancer are the small molecular inhibitors of the internal tyrosine kinase domain of the EGFR – erlotinib and gefitinib, sometimes referred to as EGFR TKIs. In some NSCLCs, especially adenocarcinomas, tumour growth and progression appear to be driven by a mutated EGFR tyrosine kinase, which activates downstream KRAS, STAT and AKT/PI3K pathways without EGFR ligand binding. Such EGFR mutations appear to be mutually exclusive of other potentially important tumour-driving mutations such as those found in KRAS or BRAF. Tumours dependent upon an exclusive, activating EGFR mutation have been described as demonstrating 'oncogene addiction'. Deletions in Exon 19 and a point mutation (L858R) in Exon 21 account for around 90% of mutations reported in the EGFR TK domain; these and a range of others are associated with sensitivity to TKI therapy. Exon 19 deletions probably confer greater sensitivity to these drugs than does L858R. Around 5% of described mutations, especially in Exon 20, are associated with resistance to TKI therapy. It is thus important to identify the precise nature of any mutation present.

The clinical response to these drugs in patients with tumours bearing sensitising mutations can be spectacular. The symptomatic and survival benefits in NSCLC from erlotinib as second-line therapy (after progression following chemotherapy) has been known for some time. Recent publications have demonstrated excellent responses to gefitinib in patients who are chemo-naive and it is now licensed for use in first-line treatment. Not only was the progression free survival on gefitinib significantly improved in patients with an EGFR-mutated tumour when compared with standard cytotoxic chemotherapy; it is also clear that patients without EGFR mutation did significantly worse when treated with gefitinib rather than chemotherapy.

These exciting developments in lung cancer pose interesting problems and opportunities for testing laboratories and pathologists. For a variety of reasons relating to tumour location and patient co-morbidity, the acquisition of good-sized samples from lung cancers poses challenges for clinicians. In the majority of cases the tumour samples available for diagnosis of lung cancer are extremely small, comprising few tumour cells admixed with non-neoplastic cells in the tumour stroma and adjacent tissue. The majority of the tissue will be 'fixed' in formalin and processed into a paraffin tissue block to allow for microscopic examination, identification and classification of any lung cancer present. Increasingly, immunohistochemistry is used on tissue sections to assist in tumour subtyping.

Subsequently, the small amount of tissue remaining must now be used, in appropriate cases, for EGFR mutation analysis and, in the future, other molecular tests especially if the EGFR mutation is absent.

In terms of molecular testing the low overall yield of often poor quality DNA, in addition to the dilutional effects of non-neoplastic genome and the potential for mutation heterogeneity in tumours pose technical challenges. The proportion of the sample

"The infrastructure of diagnostic molecular genetics laboratories together with trained and experienced personnel is already in place."

which is mutant, assuming EGFR mutation is present, will depend to some extent on the percentage of tumour cells in the tissue submitted for analysis. It is therefore of vital importance that an assessment of tumour content is made by the pathologist, followed by micro or macro dissection to enrich for tumour where necessary.

While direct sequencing may be the 'gold standard' methodology, there are issues around test sensitivity. Identification of mutations at very low levels may be possible using a variety of other techniques but care is required in the use of such approaches, and particularly in the interpretation of the result. The clinical significance of EGFR mutation detection is predicated on the outcomes of several clinical trials which used high sensitivity techniques such as ARMS and fragment length analysis. In these publications, however, researchers set relatively high thresholds for tumour quantity in the sample or confirmed the mutations found by direct sequencing. The implementation of various high-sensitivity techniques, driven by an understandable desire to provide quick results on tissue samples bearing very low percentage and absolute numbers of tumour cells, risks detection of mutations of uncertain clinical significance and increases the chance of false positive results. While false negative results may occur if lower sensitivity tests are used in conjunction with tissue containing little tumour, a false positive test has a far greater negative impact on the patient in terms of inappropriate treatment.

Mutation testing will have cost implications, both financially and through 'consumption' of probably limited tumour tissue. Simple pre-screening strategies may have a role in identifying tumours that do NOT have EGFR mutation, preventing unnecessary testing and use of tissue, which may, in the future, be required for other mutation or biomarker analysis. One example might be to test initially for KRAS mutation. This may also be useful as a negative indicator for TKI therapy.

This is just the beginning of more extensive genetic analysis to determine the most appropriate treatment for lung cancer patients. Considerable care and expertise are required to deliver a safe, accurate and consistent diagnostic service. Existing expertise amongst pathologists and molecular biologists / geneticists must be applied in a carefully integrated manner to achieve this end. A number of important issues need to be resolved so that patient treatment can be decided as quickly and accurately as possible

- Who should carry out these tests? The infrastructure of diagnostic molecular genetics laboratories together with trained and experienced personnel is already in place. Should the tests be carried out in these laboratories or should parallel facilities be developed in specialised pathology laboratories to provide the analyses?
- Best practice guidelines and Quality assurance schemes are a necessary part of such services and need to be developed.
- EGFR mutation analysis is just one example of a test which can have dramatic significance for patient treatment. There are considerable funding implications of such developments, a pertinent point in particular, when new testing facilities are proposed.

It is clear that in the UK the existing network of clinical genetics laboratories could readily provide the required molecular expertise required for this type of test but whether they will is a different question, yet to be decided. However such services are established in the future, they must be implemented to include very close collaboration and communication with appropriately trained pathologists in order to ensure the most accurate, meaningful test and therefore the best possible outcome for the patient.

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Sarah Winckless – Olympic rower

Huntington's it wasn't a word I grew up with, however I did grow up with the question 'What is wrong with your mother – she's changed so much since we saw her last'. I had no answer, and the standard reply became – 'Oh you know, that's Mum, it's just how she is.'

After the final at Athens - all I know at that point is it hurts!

So when finally, after great resistance from Mum, a diagnosis was given, it was a relief for me. There was an illness I could understand, read about, support my family in and forgive certain behaviours I saw in my mother. I also discovered I was at a 50% risk of inheriting the disease, as were my other three siblings. For me it was simple, knowledge was power and I wanted to be tested. To get a 'positive' result in my thinking wouldn't really be any different from being 'a risk', whilst a 'negative' result (not having inherited the gene) would wipe the slate clean. This second scenario was not to be, I had inherited the gene – I was 23 years old, a Cambridge Undergraduate and a keen sportswoman.

I was extremely lucky with the support I received from friends, family and the staff at the Brain Repair Centre at Addenbrookes, many who are now counted in that first category. After a typical, if fairly rapid grieving and acceptance period, (life was busy and now I had even more excuse to cram a couple of extra things in) I finished my university career and moved on to a new challenge. I had taken up rowing during my stay at Cambridge and decided to see how far I could take the sport. Lottery funding for athletes had just been introduced, and if I could be good enough, I would be supported financially to become a full time athlete. It only took me months to be accepted on the national programme, and within two years I was at my first Olympic Games. However it took years, hours and hours of training and many disappointments to become a consistent medal winner. After some frustratingly close fourth and fifth places, I finally achieved an Olympic Bronze medal and two World Championships in my eleven year career.

Sharing the moment with Mum

For some of this time my Huntington's status was in the background, known only to a few, but with Mums progress a constant reminder of the impact of the condition. She walked unsteadily but stubbornly around the stadium during Sydney 2000, four years later in Athens she was in a wheelchair, but was still very much able to be part of the event, my medal and the celebrations. I was given the opportunity to do some press about the disease and what it might mean for me in the future, and after careful consideration I decided it could only do good to raise awareness of this relatively unknown condition.

Having taken this step other opportunities have come my way and I continue to try and do my bit to raise awareness. I have had the privilege of being made Patron of the Scottish Huntington's Association in this, their 20th year. In this role I've got to be involved with the launch of the UK and Ireland Huntington's Alliance, meeting the president of Ireland, Mary McAleese, and English patrons Tony Hadley and Shane Ritchie. I have worked with young people who are caring for family members and might be 'at risk' themselves, at a dedicated youth camp, and spoken with families at conferences. I don't pretend to have the answers and I can only give my opinion and experience, but I try and promote a positive attitude and healthy living, which can only help for a better future. Finally, in this busy year I was tempted out of retirement by a friend Vic Wood and we raced at Henley Women's Regatta to raise awareness and money for the Huntington's Alliance. Our goal was to raise £1000 a day for 10 days in a short campaign linked to Huntington's Awareness week. We were blown away by the response, topping the £30,000 mark in that time.

So what comes next? At 36 I have finally entered the real world, running my own company, motivational speaking, life coaching and working on team building. I try and do some exercise every day, and keep looking for new and exciting physical challenges to excite and motivate me!

Relaxing by the river

Human Genetics Commission consultation on direct to consumer genetic testing

Chris Patch, Chair, BSHG

Background

The Human Genetics Commission has published two reports on direct to consumer genetic testing: Genes Direct and More Genes Direct. These reports were in response to concerns about a growing and unregulated market in this area. One of the recommendations arising from More Genes Direct was the development of a framework of principles which might act as a high level document which could be used as the basis for legislation or codes of practice.

The principles cover all aspects of direct-to-consumer genetic testing services including the marketing and advertising of tests, information for consumers, consent, the laboratory analysis of biological samples and the levels of support that should accompany the genetic test results.

A consultation was carried out towards the end of 2009 and the response made by the BSHG is printed below. There is due to be another meeting shortly to further develop this framework. The full consultation is available from the HGC website http://www.hgc.gov.uk/Client/document.asp?DocId=214&CAtegoryId=3

BSHG response

This response is submitted on behalf of the council of the British Society for Human Genetics. The BSHG is an independent Society representing professionals working in the field of human genetics. The BSHG is formed of a number of individual constituent groups and societies who along with individual members may have made their own responses.

The excitement about the potential benefits arising from genetic research leading to the potential to offer personalised and predictive medicine, together with the development of an essentially unregulated market in the offer of 'tests' directly to the consumer has proven to be extremely challenging. It is timely that the HGC has endeavoured to produce a framework of principles in this area to provide some element of assurance to the consumer. This framework would seem to be an appropriate and pragmatic response which attempts to provide a level of assurance without being overly restrictive. There are wider areas of concern in the regulation and provision of laboratory diagnostics which are not part of the remit of this consultation but which do have a bearing on the provision of genetic testing services. The focus of the recommendations on quality assurance of laboratory processes, evidence of scientific and clinical validity and the need for appropriate information applies more generally across testing service as well as in this specific area.

Questions in relation to the levels of support that should accompany genetic testing.

1. Do you believe that recommending individualised pre- and post-test counselling to accompany genetics tests in the context of inherited or heritable disorders is the right approach?

For certain categories of tests as outlined in the consultation document there is agreement that individualised pre and post test counselling is desirable in order that people may make an informed decision and be supported in the consequences of that decision. Some potential qualities of genetic information in the context of heritable disorders are the implications for the extended family and also the prognostic information that may arise. For example diagnostic testing for the breast cancer predisposition genes BRCA1 and 2 used to be offered without much pre-test counselling. It became apparent that many women found the knowledge of a genetic fault very difficult as despite the fact they had already had breast cancer they were not aware of the family implications and the implications for their personal risk of future new cancers should a mutation be identified. It is important that the counselling should be provided by a suitably qualified and experienced person.

2. Do you believe there are certain genetic tests that should not be offered direct-to-consumers? If so, which categories of tests?

If the principles in relation to levels of support that should accompany genetic testing are applied and if it can be assumed that responsible providers would want to comply with those principles then the genetic tests should be provided within accepted international and national guidelines. There should be consistency in standards and care across all providers. However there are some problems in relation to how the tests are defined by the current providers in the market. There is confusion as to whether the test is simply information in the form of a sequence or SNP analysis or whether it is health related information such as a mutation in the BRCA gene. There is scope for test providers to argue they are not providing a medical service and therefore standards applicable to medical services do not apply. In this scenario it

"Once pharmacogenetic tests have established utility they will be part of effective prescribing in routine practice."

is useful that the Framework attempts to provide a context based justification for the level of oversight required.

Questions in relation to stratification of the principles

3. Pre-symptomatic and susceptibility/pre-dispositional health tests are distinct categories in the draft of the Principles. Do you believe that this distinction is both valid and robust? If not, do you believe these two groups of tests could be stratified better?
This is a very difficult area in which to make clear distinctions. Although in a naïve way it can be seen that there is a clear distinction between susceptibility and presymptomatic as outlined in the question it is difficult to establish where the division is actually made. The 'risk' associated with any test in the sense of potential harm is a complex interaction between the epidemiological risk, the consequences, the consumers experience and characteristics and the potential interventions that may ameliorate those risks. Whatever the actual lifetime risk it is important that the consumer is given the appropriate information in relation to the clinical and scientific validity and the possible utility of the information they receive. If commercial providers are willing to endorse a common framework of principles then they perhaps would be able to stratify the 'seriousness' of the test and as part of the compliance with the principles only offer the 'high' risk test with appropriate pre and post test support.

4. Should the Principles recommend that pharmacogenetic tests only be provided to consumers with individualised pre- and post-test counselling and should they fall into the bracket of 'genetic tests in the context of inherited or heritable disorders'?
Once pharmacogenetic tests have established utility they will be part of effective prescribing in routine practice. DTC tests may be taking place outside of this linked intervention however the information provided should strongly endorse the necessity of discussion with a medical practitioner before changing prescribed medication. In reality non-compliance with prescribed medication is more of a problem and while the results of a DTC test may provide an additional justification for non-compliance recommendations for a medical discussion may encourage compliance with an alternative therapeutic regime.

5. Are the impact criteria listed in Principle 10.1 (in addition to the categorisation of tests) a helpful additional way of stratifying genetic tests? Should a list of test be included in the Principles that determine to which genetic tests the application of Principle 10.1 is relevant?
It is helpful to characterise the qualities of the tests that drive its categorisation. This would make the framework more future proof as a list could quickly become out of date. However the decision making process would be aided by including examples of specific tests with each category. If there was a mechanism for agreeing a list of tests within such a framework then addition to that list should be possible providing the framework was consistent. If tests are being performed that do have implications for extended family, significant risk to future health or possible interactions with other drugs and diseases then it would be preferable that this forms part of the consumers' medical record. Clearly however this would have to be at the instigation of the consumer.

6. Are there any principles that are applicable to certain genetic tests that you consider should not be applied to that test? Specifically, do you consider the amount of information that test providers will be expected to provide to consumers to be excessive for some tests?
The framework should set out a minimum standard of core information that applies to all tests and this list in question 6 would seem to be appropriate. This is analogous to the prescribing information provided with drugs. If the framework is adhered to then the categorisation of tests according to their impact together with the provision of appropriate pre and post test counselling support to the higher risk category would provide an extra level of information over and above the minimum standards.

For governance and consumer protection if the test is providing medical information it would seem to be essential that there is accountability to a named person to whom appropriate sanctions might apply if they fell short of professional standards.

Questions in relation to consent

"The provision of this framework of principles would seem to be a flexible and pragmatic approach to this issue."

7. Should Principle 5.10 be included? (Genetic testing of children)
There is a general agreement amongst the genetic community that although there is a move away from a very prescriptive position, a child's autonomy in relation to their potential future should be protected. If the test result provides no benefit now then the decision would be the child's when he/she is in a position to make it. Therefore principle 5.10 should be included and the presumption should be that childhood testing should not be performed unless it is to the child's benefit. In clinical genetic practice where childhood genetic testing may be performed for the benefit of the child e.g. testing for the polyposis gene in order to avoid unnecessary screening, the challenges of providing age appropriate information and counselling is well recognised. It is also not clear whether in fact there may be the possibility of a future claim by a child should the result of a test lead to some harm such as misinterpretation of the result leading to undue anxiety or investigations or even failure to access insurance or difficulties with employment.

8. Principle 5.3 states: "The test provider should take reasonable steps to assure themselves that a biological specimen provided for testing was obtained from the person identified as the sample provider. They should obtain a signed statement to this effect from the person buying the test".
What do you consider to be 'reasonable steps' and should the Principles state what these steps should be?

As stated it is always going to be difficult when testing at a distance to absolutely ensure that no fraud has been carried out. While a signed identity statement may seem to confirm identity it would be relatively easy to circumvent and it is difficult to know how any measure would prevent fraudulent testing. However that does not mean that the issue should not be raised in pre test information and counselling and that consumers should explicitly be made aware of any legal sanctions applying in their jurisdiction.

9. After discussions within the working group the following principle was not included: "A test provider must take whatever measures are necessary and appropriate to ensure that an individual has provided informed consent and has capacity to provide that consent for a genetic test." Do you think this principle should or should not be included?
If principles 1.3 and 10.1 are included in the framework then this would appear to be redundant.

Other questions

10. Are any of the principles impossible to apply in your jurisdiction given existing national legislation or regulatory constraints?
We are not aware of any regulatory constraints that could affect implementation of the principles.

11. Do you believe that test providers should sign up to the Principles and what costs do you expect will be incurred by complying with the Principles?
The main costs to the provider may be the provision of face to face counselling and potential liability for harms caused by failure to apply the principles. There is the possibility that there will be extra costs to health services as a fall out from these tests, however this is difficult to predict. In order to ensure equity of access it would be important that a mechanism exists to introduce tests of proven benefit into health care systems in a timely fashion. The exact mechanism for this is an issue outside of the scope of this framework however.

The provision of this framework of principles would seem to be a flexible and pragmatic approach to this issue. Whilst legislation would provide the greatest protection it is time consuming, would not apply across all jurisdictions and given the fast moving pace of developments ion this area would very quickly not be fit for purpose. The advantage of a pragmatic framework that is not unrealistically restrictive may be that reputable DTC providers will see a commercial advantage to a mark of quality. The framework could be used to identify gaps in for example existing consumer regulation that may be more amenable to legislative processes.

House of Lords Enquiry into Genomic Medicine

Chris Patch, Chair, BSHG

The culmination of an eighteen month enquiry into Genomic Medicine by the House of Lords Science and Technology Committee was published in July 2009.

http://www.publications.parliament.uk/pa/ld200809/ldselect/ldsctech/107/107i.pdf

The Committee heard evidence from a wide variety of relevant individuals, groups and Societies including the BSHG. The report made a number of recommendations, including a call for a new White Paper on Genetics. The Government's response was published in December.

http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_110005.pdf

In this response they have supported the setting up of a cross-department genomics strategy group but rejected the recommendation for a new White Paper.

BSHG Council has made the following comments:

The House of Lords Report on genomic medicine argued that the rapid development in genetic science requires new strategy for its delivery within health services and research. The government's response largely restates past achievements and seems to suggest that minor modifications of current processes will allow delivery of the benefits of advances in knowledge.

The enquiry into genomic medicine was a thorough and time consuming report which brought together many experts from across the field. It is encouraging that the Government in its response has made a commitment to establish a Human Genomics Strategy Group which will work across departments. The British Society for Human Genetics will strongly support this initiative.

The establishment of a new diagnostics committee through NICE is also potentially useful. A significant thread running through the Report was the difficulty of implementation of new diagnostics in a timely fashion. The Response to recommendations regarding commissioning of genetic tests however was disappointing. Current locally devolved models of commissioning and delivery are already failing to deliver equitable access to genetic tests for the rarer disorders. As molecular tests become useful across medical specialties this gap can only increase and expectation that improvements will be delivered through existing models and World Class Commissioning without any clear steer is a missed opportunity. It is to be hoped that the cross-departmental Human Genomics Strategy Group is able to explore this as a priority.

The BSHG will collaborate in the efforts to bring the expertise and experience and infrastructure of genetic and molecular pathology laboratories closer together in order to develop sustainable delivery models for the future. We also welcome the Government's commitment to establish an Institute of Biomedical Informatics and will help develop the concept of an organisation to enable the NHS to develop bioinformatic capability within its current staff. This would include developing the best ways to access bioinformatic expertise and the necessary infrastructure to process, analyse and integrate medical data from new analytical technologies with the most appropriate and secure mechanisms to store and access the data. The BSHG would also want to work with the Research Capability Programme of Connecting for Health to facilitate the development of robust consent procedures and appropriate research access to data sets generated by clinical and laboratory genetic services. We are already represented on the Genetics IT Development Group in CfH and will continue to work with the group to develop data standards for Genetics IT systems. However as before the government response does not seem to recognize the urgency of the need for developments in this area or the magnitude of the task.

The BSHG is working as part of other groups to present a commentary and response to the original Report and the Government Response which deserve more detailed and considered thought. Whilst accepting that the current economic climate means that increased investment is unlikely, there is a need for strategic direction to ensure that effective developments are adopted and delivered equitably.

Delivering better care for families with inherited cardiovascular conditions

Dr Philippa Brice and Dr Hilary Burton, PHG Foundation, Cambridge

Inherited cardiovascular conditions (ICCs) are a group of more than fifty disorders ranging from relatively common conditions such familial hypercholesterolaemia and hypertrophic cardiomyopathy to much rarer disorders such as long QT syndrome. Together, inherited conditions that involve the heart affect around 340,000 people in the UK; some of these individuals are at high risk of sudden cardiac death, but most remain undiagnosed.

The impact of genetics

In the last few years, along with developments in cardiology, advances in cardiac genetics have opened new possibilities for precise genetic diagnosis, which can also inform clinical management and preventative care for patients and families - not only drug treatments, surgery or implantation of defribillators but also lifestyle advice to avoid triggering events, which vary depending on the underlying molecular abnormalities.

Cardiologists and geneticists have realised that that they need to work together to deliver the best care for patients. Earlier this year, the PHG Foundation launched Heart to Heart, the report from the first national population needs assessment and service review for ICCs to be carried out anywhere in the world. This work was funded by the PHG Foundation, and carried out in conjunction with an external Working Group of experts, including NHS cardiologists, geneticists, service commissioners and managers and representatives from patient groups and charities the British Heart Foundation (BHF), Cardiac Risk in the Young (CRY), the Cardiomyopathy Association, the Marfan Association UK and Sudden Arrhythmic Death Syndromes (SADS) UK.

Limitations of current care

A survey of NHS service providers revealed insufficient capacity to meet current or projected future needs, and found serious inequalities in the quality and quantity of services available to patients in different parts of the country. The group made recommendations for developing and delivering up-to-date specialist multi-disciplinary services for ICCs, including access to laboratory and pathology testing and other clinical investigations and provision of bereavement support and counselling for families. Increased awareness of these integrated services among health professionals in both primary and secondary care, co-ordination with voluntary support organisations were also considered essential.

The report concluded that ‘every UK cardiac network should ensure that its population has access to specialised expert ICC services for children and adults’, although most will not have their own service. Other key recommendations included the need to develop a workforce with the necessary specialist competences, to develop new systems of cascade testing, to keep abreast with emerging research, and to seek legal and system changes to ensure appropriate retention and handling of tissue samples following sudden cardiac death. This would include clarification of the responsibility of coroners to family members who may be at risk of ICCs.

Towards an integrated multi-disciplinary service

The UK Department of Health is now taking forward the recommendations for developing and delivering up-to-date specialist services for ICCs. A framework for commissioners has been developed and work on standards is planned. Cardiovascular genetics also provides a useful paradigm for other clinical services where advances in understanding of molecular mechanisms can enhance services for people with inherited conditions.

The report is available for free download from: www.phgfoundation.org.

For further information, contact Corinna Alberg: corinna.alberg@phgfoundation.org

Needs assessment and review of Tay Sachs disease carrier screening in UK Ashekanzi Jewish populations

Dr Philippa Brice and Dr Hilary Burton, PHG Foundation, Cambridge

Carrier screening for TSD in the Ashkenazi Jewish population was accepted in principle by the National Screening Committee in 1999 and placed broadly within the antenatal screening programme. Since then, testing has been provided by NHS laboratories with support from regional clinical genetics services. It is also available privately. However, a full NHS antenatal carrier screening service for TSD such as those for sickle cell disease and thalassaemia has never been established. When in 2004 a national meeting was held to discuss the addition of further 'Jewish' conditions to the panel, it was recommended that the functioning of the current Tay Sachs service should first be reviewed

In a joint project commissioned by the UK Newborn Screening Programme Centre, a team from Guy's and St Thomas' NHS Foundation Trust Clinical Genetics Service and the PHG Foundation in Cambridge, working with an expert advisory group, produced a needs assessment and review of screening services for Tay Sachs Disease in the UK earlier this year. This also included a literature review and evaluation of the two alternative testing methods (molecular and enzyme based testing).

Current screening services

The carrier frequency for the autosomal recessive degenerative neurological condition Tay Sachs disease (TSD), which causes death in early childhood, is substantially increased in Jewish Ashkenazi populations at around 1 in 27. Testing allows individuals identified as carriers to reduce their risk of having a child affected by TSD, and carrier screening is used by couples and, in some communities, forms part of the process for arranging marriage introductions.

The main carrier testing service is a weekly walk-in clinic at Guy's Hospital in London, for which clinical referrals are not required. Testing is available through NHS laboratories in London and Manchester (Guy's Hospital and Willink Laboratory). Outreach screening sessions to schools and other Jewish communities are also provided by Jewish voluntary organisations. The overall carrier frequency for TSD for the combined services was greater than 1 in 27.

A survey of antenatal screening coordinators as part of the review showed that antenatal screening was not systematically offered, even in areas with substantial Jewish populations. There was a lack of clear or consistent protocols or pathways for antenatal TSD carrier screening, and confusion about whether women should be asked about Jewish origins. A patient survey of individuals arriving at the Guy's clinic revealed that awareness of (predominantly Ashkenazi Jewish) ethnic origins was high, but most found out about carrier testing from family, friends or the internet rather than via health care professionals. One third of patients undergoing testing were pregnant, and half of these were in the second trimester of pregnancy.

Conclusions and recommendations

Jewish couples need access to TSD carrier testing via the NHS, but there is currently no systematic provision of such services. There is an outstanding need for clear policy on TSD carrier testing in NHS services nationally (at the level of the National Screening Committee and commissioners of regional services), and locally for areas with substantial Jewish populations. The working group's report to the National Screening Committee set out measures that would be necessary to develop TSD carrier testing as a robust screening programme.

However, there currently remains a debate at National Screening Committee level as to whether the service should be offered on a case-by-case basis only to those who request it as opposed to via a formal screening programme and, further, whether a national programme should include preconceptual as well as antenatal screening. The latter issue is expected to be progressed through joint work between the Human Genetics Commission and the National Screening Committee. In the immediate term, however, antenatal services urgently need to clarify their response to women at high risk of TSD and those who express concern about the condition, and to educate midwives and screening coordinators to ensure that women receive appropriate care and advice.

The report is available for free download from: www.phgfoundation.org.

For further information, contact Corinna Alberg: corinna.alberg@phgfoundation.org.

Reducing the risk of prenatal diagnosis by developing non-invasive prenatal diagnosis based on cell free fetal DNA in maternal plasma –RAPID programme update and how you can help

Mel Hill and Lyn Chitty on behalf of RAPID

Overview of the RAPID programme

RAPID - Reliable Accurate Prenatal non-Invasive Diagnosis is a 5 year UK national programme funded by the National Institute for Health Research. The aim of RAPID is to improve the quality of NHS prenatal diagnostic services by evaluating early non-invasive prenatal diagnosis (NIPD) based on cell free fetal (cff) DNA and RNA in maternal plasma.

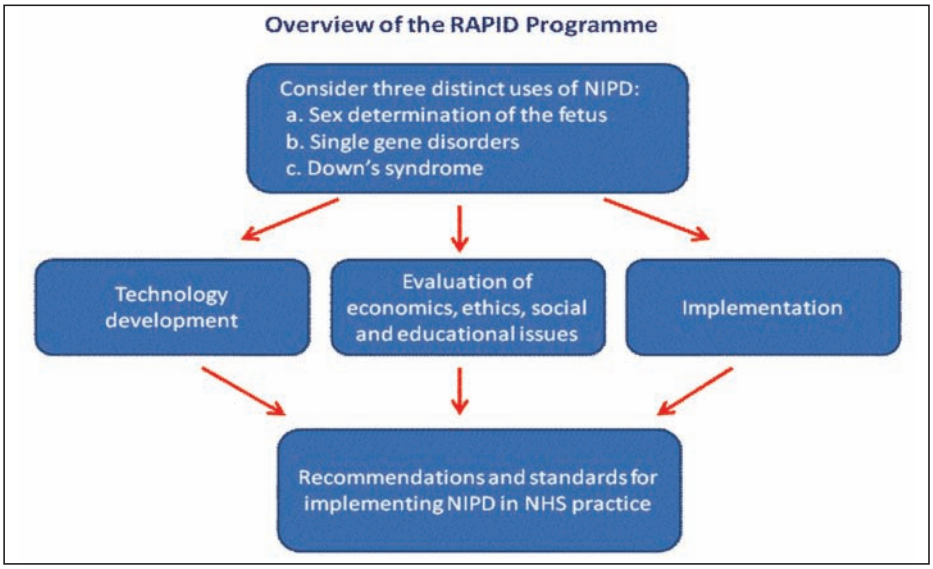
Currently, prenatal diagnosis of genetic and chromosomal conditions involves invasive testing, such as amniocentesis or CVS, performed from 11 weeks gestation and carrying a 1% miscarriage risk. The identification of cffDNA and cffRNA in maternal blood offers an alternative earlier and potentially safer source of fetal genetic material for prenatal diagnosis. Prenatal testing based on cffDNA and cffRNA represents a steep change in practice. NIPD will use different laboratory procedures and will require investment in new equipment, the development of new laboratory skills, standards, quality assurance etc. It will also need a different approach clinically, particularly in respect to counselling. The ethical and social implications of the potentially easier access to non-invasive testing may also be significant.

As NHS laboratories are already experimenting with NIPD there is an urgent need for a formal evaluation to develop quality procedures and appropriate, safe health care delivery systems accounting for patient preference and yet minimising risks to families from improperly implemented new technologies before it just 'seeps' into practice. The overall goal of the RAPID programme is to develop a cogent set of recommendations for use by those implementing NIPD in NHS practice which embraces the needs and opinions of all stakeholders involved in service provision – health professionals, commissioners, pregnant women, their partners and the wider community.

Much of the work in the RAPID programme will continue from research done during the successful SAFE EU Framework 6 network of excellence which ended in February 2009. SAFE aimed to facilitate the development of NIPD in Europe. The large bank of samples collected by SAFE will be used in the early stages of the laboratory arm of the RAPID project. We will also build on the preliminary work done by the SAFE ethics work package and the Genetics Interest Group (GIG) describing the impact on pre-test counselling and the lay public needs.

Our specific research goals

- Build a bank of maternal, paternal and fetal samples from pregnancies at risk of single gene disorders, aneuploidy or obstetric complications that can be used by laboratory groups developing NIPD technologies.
- Develop laboratory standards and quality assurance for NIPD of fetal sex determination, single gene disorders and Down's syndrome.
- Evaluate the cost effectiveness of NIPD to assess whether it represents good value for money for the NHS and for pregnant women and their families.
- Determine couples' choices, preferences and needs and evaluate health professional's attitudes.
- Assess wider social and ethical issues.
- Develop educational material for families, health professionals and the general public.
- Provide recommendations for implementation.



"The bank of samples now exceeds 1600 and includes cases from a range of aneuploidies and single gene disorders."

Our progress to date

- RAPID was launched on July 7 2009 at the Institute of Child Health in London. The launch featured a series of seminars and discussion forums that covered current practice in NIPD, the objectives of RAPID and the need for help from health professionals, the public and other stakeholders. This successful meeting was attended by more than 200 stakeholders from a range of disciplines.
- The bank of samples now exceeds 1600 and includes cases from a range of aneuploidies and single gene disorders. These samples are currently being used by a number of laboratories to investigate aspects of NIPD, explore methods of plasma preparation and storage, to establish services in individual laboratories and to develop new assays as outlined in the original proposal.
- The PROOF (Prospective Register of Outcomes Of Free fetal DNA testing) audit is ongoing. In the first year of the audit (2006-7) there were 6 of 161 results of fetal sex determination using cffDNA which gave discordant results. Subsequent to these result the laboratories involved in the audit altered their practice. We have continued the audit and are currently collating the outcomes for 2007-9. Over 75% of outcomes have now been returned from 584 cases. In 324 pregnancies where a result has been issued and we have the outcome, no discordant results have been reported. No results were issued in around 4% of cases because laboratory reporting standards were not met. Full results of the audit will be published as soon as all the outcomes are returned. This audit covers all cases where fetal sex determination is requested from the IBGRL in Bristol (using DYS14) and the North East Thames Regional Genetics Laboratory at GOSH (using SRY).
- A RAPID Dissemination meeting for laboratory heads will be held in January at the Institute of Child Health in London. This meeting will be a forum for discussion of advances in laboratory technologies, highlight work which is ongoing in this area around the country and help us develop collaborations to expedite the research and subsequent implementation.
- A number of centres around the UK including several in London, Wessex, Newcastle and Manchester are now coming on board to be collaborators on RAPID and help with recruitment.
- The economic, psychosocial and ethical workstreams are underway and will begin with a series of focus groups with people who may consider taking up NIPD if it was available for single gene disorders such as cystic fibrosis or sickle cell anemia.

Your collaboration in RAPID is invited

The success of this project depends on collaboration from a wide range of health professionals from genetics, maternity and fetal medicine units around the UK as well as pregnant women and their partners, commissioners, policy makers and the broader general public.

We are currently seeking help from maternity and fetal medicine units to help us collect samples from pregnancies undergoing invasive diagnostic testing. We hope to collect parental blood samples from pregnancies at risk of single gene disorders, aneuploidy or obstetric complications that may compromise fetal well being.

Ethics for the collection of samples has been approved and all study materials have been prepared. A member of the RAPID team will work with your unit to organise the site specific approvals and to set up recruitment and dispatch of samples to suit the unit's specific needs. We are also very happy to come to your units to explain what is happening and how you can help.

Where to go for further information

If you have any questions about RAPID or would like to help with the research, please email us at rapid@ich.ucl.ac.uk.

The RAPID website at www.rapid.nhs.uk is expanding. It gives more detailed information RAPID and has a growing library of NIPD references. As the project progresses there will be more information added.

The Rapid Team

Lyn Chitty, GOSH, UCLH, UCL
Principal investigator, Fetal medicine, genetics, implementation

Douglas Altman, Centre for Statistics in Medicine, Oxford
Statistical supervision

Neil Avent, University of Plymouth
Laboratory development

Hilary Burton, PHG Foundation
Public Health advice

John Crolla, Wessex Regional Genetics Laboratory
Service laboratory development, strategy

Rob Elles, NGRL Manchester
Laboratory standardisation

Peter Farndon, National Genetics *Education centre Education, clinical genetics, policy*

Mel Hill, GOSH and UCLH
RAPID programme manager

Nowgen brings world-leading genetics research into schools

Leah Holmes, Nowgen, Manchester

Human genomics, the study of genetics and the human genome, is poised to become part of UK science lessons thanks to a new programme launched by Nowgen. The 'Nowgen Schools Genomics Programme' will bring cutting-edge scientific research into schools, exciting pupils about the pace of discovery and engaging them in thinking about how advances in genetics will affect their future lives.

Traditionally, it can take 10 years or more for new scientific discoveries to become integrated into science teaching. Nowgen's Schools Genomics Programme aims to address this - narrowing the gap between genomics research and classroom genetics.

The project, funded by The Wellcome Trust, will include seminars for examiners on the latest developments in genomics and healthcare, offer students opportunities to visit research establishments and result in the production of three new Teachers TV programmes for students and teachers. The innovative three-year programme will be run by a team of Nowgen clinicians, scientists and educationalists.

As well as influencing how genetics is taught in schools, the project will look at new ways of integrating contemporary content into traditional science and within science related courses such as A-level Science in Society and The History and Philosophy of Science.

Peter Finegold, leader of the Schools Genomics Programme said: "Every day we read stories in the newspapers about how scientists have found genetic predictors for common diseases, such as cancer, diabetes and rheumatoid arthritis. Nowgen's Schools Genomics Programme will help young people to interpret what these news stories are saying, by providing greater insight into the complexity of the science, and into the implications on our society of applying this knowledge in a healthcare context."

The project team expects to see some of the outcomes of its work included into GCE A-level specifications in England within the next five years and hopes it will be included in the major review of the GCSE science curriculum, due to be carried out in 2011. Early discussions are also underway with key curriculum developers in Scotland.

Death row prisoner, exonerated by genetic testing, speaks in Manchester

Helen Middleton-Price, Nowgen, Manchester

John Thompson and Emily Maw

John Thompson, an American death row prisoner whose murder conviction was quashed after seven stays of execution, was invited by Nowgen to visit Manchester in October to talk about his experiences.

The visit had been organised by Helen Middleton-Price from Nowgen, who earlier this year gave a talk to the University about her experience working on sabbatical for the charity Reprieve at the Louisiana Crisis Assistance Center in New Orleans, which represents prisoners on Death Row in the southern states of the USA.

In 1985, John Thompson, from New Orleans, was convicted of first degree murder and an attempted carjacking. The 24-year-old father of two was placed on death row in Louisiana's notorious Angola prison where he spent 23 hours a day in a 9ft by 6ft cell contemplating the prospect of death by lethal injection.

Nearly 600 people attended John's spellbinding presentation to hear how just days before he was due to be executed, having exhausted all his appeals, an investigator re-examining the carjacking uncovered a laboratory report that cast doubt on his conviction, showing that the attacker had a different blood type. This evidence, it would later emerge, had been deliberately withheld at John's trial. At a re-trial in 2003 in the Court of Appeal a jury took just a few minutes to acquit him of murder. The real killer could not be pursued as the garment from which the blood sample had been taken was mysteriously 'lost' from the evidence box.

John joins the increasing number of men in the USA who have been exonerated following wrongful conviction; new developments in DNA analysis have resulted in 245 post-conviction DNA exonerations in the USA, of whom 17 have spent time on Death Row. Following his release from 18 years behind bars, John was awarded £14 million dollars in compensation, but he has yet to see a penny of it. In spite of this, he founded a charity, Resurrection after Exoneration, which helps men like him who are victims of miscarriages of justice.

Some of the 600 people who came to hear John speak

John was accompanied on his visit by British-trained lawyer Emily Maw, the Director of Innocence Project, New Orleans. John and Emily's presentation was chaired by Mark George QC, a well-known Manchester human rights lawyer. The visit resulted in substantial media coverage, including interviews with The Independent and BBC Breakfast.

A member of the audience asking John a question

For more information about Reprieve, Resurrection after Exoneration or Innocence Project New Orleans, please contact Helen at helen.middleton-price@cmft.nhs.uk

Engaging the public in debating childhood obesity

Leah Holmes, Nowgen, Manchester

Dr Chris Steele

On 28 October 2009 Nowgen, A Centre for Genetics in Healthcare, welcomed an enthusiastic audience to a fascinating public debate into childhood obesity in England. The event was organised as part of the Manchester Science Festival, to explore attitudes towards this serious health issue which has gained increasing focus in recent years.

The audience discussed wide-ranging issues with an expert panel, and voted electronically on key questions throughout the evening. Possibly the most controversial finding was that, 22% of the audience think that obese people, rather than taxpayers, should pay for their treatment on the NHS.

Led by Dr Chris Steele, GP from ITV's This Morning, the panel of experts included Dr Catherine Hall, paediatric consultant, from Manchester's Biomedical Research Centre, Professor Andrew Hill, obesity psychologist from The University of Leeds, and Vicki Swinden, founder of Fat is the New Black.

Dr Hall researches childhood obesity and has recently involved young obese people in developing a regional obesity service tailored to their needs. Her presentation discussed the link between obesity and genetics. "We now know that the condition can be a result of the interaction between environmental factors and a genetic predisposition. 84% of overweight children have a family history of obesity and there is more to it than just eating too much and exercising too little."

As well as the general public, the audience included employees of the University and the Central Manchester University Hospitals, members of regional NHS Primary Care and Hospital Trusts, local city councils, NHS Direct and the National Institute for Clinical Excellence (NICE). Commenting on the event, Nowgen's Director of Public Programmes, Bella Starling said "These debates provide a valuable forum for a range of voices to be heard and a variety of opinions to be expressed. Sharing dialogue ensures public views contribute to medical research."

Audience member Tom, a teacher from Oldham, was surprised by what he learned during the debate; "Before this event I didn't realise that obesity was quite such a major threat to the wellbeing of young people in England. It is clear from the statistics and issues raised this evening that we need to take the problem very seriously and act quickly to ensure the good health of our future generations".

Statistics highlighted by the panel included:

- More than 28% of children in England are obese or overweight.
- 97% of obese children have parents who are obese or overweight.
- 8 out of 9 parents with overweight children do not recognise that their child is overweight.
- If left unchecked, 90% of adults will be overweight or obese by 2050

MEN Passports

Jo Grey, AMEND

UK registered charity, the Association for Multiple Endocrine Neoplasia Disorders (AMEND) recently launched its MEN Passport as the latest initiative for supporting patients with MEN 1, 2a, 2b, FMTC and sporadic MTC.

Housed in tough A5 polypropylene covers and each coming with its own AMEND pen, the Passports are built to last and contain everything a patient may need to help them navigate the maze of living with MEN, making them invaluable in the NHS move towards personal care planning for patients with long-term conditions.

Inside, the file is divided into sections where patients will find plenty of places to record contact details, their and their family's medical history, and questions for and discussions from their outpatient appointments. In addition, there are simple tables for patients to record their current medication as well as the dates, types and results of tests and scans, together with details of treatments received or planned.

The Department of Health's Questions to Ask leaflet is included in the information slot at the back of the folder, together with an AMEND clinic leaflet and, once updated, a CDRom containing a full AMEND patient information book.

The Passport project involved input from patients, the AMEND medical advisory team and endocrine nurses. In particular, patients shared how frustrated they feel when they are asked to repeat their medical story to different doctors, or when they are asked to recite their long list of current medications. The MEN Passports have addressed this and the feedback from

Update from the National

Wessex

Next Generation Sequencing. The development of new (2nd generation) sequencing technologies holds great promise for molecular genetic diagnostics both in terms of the current workloads and facilitating new tests that have previously been uneconomic or impractical. NGRL(W) is currently involved in a collaborative project with the CMGS to evaluate the utility of these technologies for diagnostic applications. The aims of the project are to stimulate dialogue between suppliers of next generation sequencing technologies and the diagnostic community, to evaluate all aspects of sample processing and data analysis, and to provide a background for collaborative development of diagnostically tailored applications. For further details please contact chris.mattocks@salisbury.nhs.uk

Reference materials. We heard very recently that the BCR-ABL freeze dried cell dilutions we made in conjunction with the National Institute of Biological Standards and Control (NIBSC) have been approved by the World Health Organization as primary reference materials for monitoring the response of chronic myeloid leukaemia patients to therapy by real time quantitative RT-PCR. We held a third meeting of UK testing labs in July 2009 and agreed further rounds of sample exchanges aimed at improving the comparability of results. A further meeting will be held in Spring 2010. For further details please contact ncpc@soton.ac.uk

Array CGH. NGRL (W) organised an international meeting in July 2009 that set out the case for the introduction of aCGH as a front line test, instead of chromosome analysis, for individuals with developmental delay or mental retardation. The meeting was attended by nearly 100 people and helped to trigger an aCGH workshop for Commissioners in November 2009, organised by Jacquie Westwood, the National Lead Commissioner for Genetics, and the UK Genetic Testing Network team (UK GTN). The meeting and workshop will hopefully facilitate equitable funding for aCGH as a replacement for karyotyping across the UK. Currently NGRL(W) is undertaking a comparison of a number of different aCGH platforms and analysis packages and we have also contributed to the International Standard Cytogenomic Array Consortium (https://isca.genetics.emory.edu/) technical and analytical guidelines that are due to be published shortly. Presentations from the meeting and array workshop are available via the NGRL (W) web site at http://www.ngrl.org.uk/wessex/array_meeting2009.html.

New Technology Meeting. We are planning to hold the fourth New and Developing Technologies for Genetics Diagnostics meeting in Salisbury on 5-6 July 2010. If you have any suggestions for topics or speakers please email ncpc@soton.ac.uk

We welcome feedback from the genetics community on our current work programmes and suggestions for future work either directly to myself, to the individual project leads or via our Steering Group. For details on all our activities at NGRL (Wessex) as well as individual contact details please see our website www.ngrl.org.uk/wessex.

Nick Cross
ncpc@soton.ac.uk

patients and their specialists has been incredibly positive.

Founded in 2002, AMEND is committed to improving the well-being of all persons affected by MEN and associated endocrine tumours by providing relevant and up-to-date information and by awareness-raising with the medical profession to assist in early and accurate diagnosis and treatment. Membership of AMEND is free to all. AMEND also runs a research registry to which the majority of patient members sign up. For more information see the AMEND website at www.amend.org.uk.

Passports are provided free of charge by return of post to all patients whether registered members of AMEND or not. They should apply direct to AMEND for a copy on 01892 520214 or info@amend.org.uk. AMEND regrets that, due to their high unit cost, Passports cannot be provided to healthcare professionals.

Genetics Reference Laboratories

NGRL
National Genetics Reference Laboratory | Manchester

Manchester

We have welcomed two new members to our team in September. Maja Milicic has joined NGRL Manchester as Bio-Health Informatics Scientist to work on clinical coding in collaboration with the Rare Disease Task Force EU-funded project led by Orphanet in Paris. Nicola Charlesworth is our new Genetic Technologist recruited to work on the RAPID Non-Invasive Prenatal Diagnosis Project lead by Lyn Chitty based at Great Ormond Street Hospital, London.

Our work in the recent months has focused mainly on the Diagnostic Mutation Database (DMuDB). In July, a new interface to the DMuDB was released to improve variant information shown on a record and enhance the submission of manual and bulk data. We have developed screencasts explaining the use of applications in the DMuDB, which are available from our website.

The first newsletter solely featuring developments around the DMuDB was launched in August. Registered users automatically receive a copy, if you are not registered but are interested in receiving the DMuDB newsletter at request.

To extend the benefit of DMuDB internationally, we are actively pursuing integration of variant data submitted to DMuDB into external LSDBs. A pilot project is under way to move MSH6 data to the InSiGHT database with permission from the submitting labs. Furthermore, a secure online service for variants potentially stored in the DMuDB was launched in October. Geneticists worldwide (who are not eligible for DMuDB registration) can submit queries regarding variants potentially present in the database. When a variant is present, details of the submitting laboratory are provided to the enquirer, so that contact can be made to request further information.

The DMuDB team continues to visit labs to introduce the database and to provide hands-on guidance in the practical use. If your lab is interested, contact us to arrange a meeting. The development and maintenance of DMuDB benefits from these interactive sessions as well, as discussion of issues experienced in the lab help us enhance services. If at any time you wish to submit variant data, but your gene is not represented in the DMuDB, let us know and we will add it for you.

In collaboration with Nowgen and the Clinical Genetics Department in Manchester, we have delivered the first bioinformatics course aimed specifically at Clinical Geneticists on the 20 and 21 October. The course was attended by 14 delegates and included presentations by representatives from ECARUCA and ENSEMBL. It was well received and we intend to run a similar course in 2010. More details will be available shortly.

Two successful and fully booked bioinformatics courses for molecular geneticists and cytogeneticists have been delivered in June and September, with a total of 40 participants. Dates for next year are 6-7 May and 14-15 October.

More information about our projects is available online:
www.ngrl.org.uk/Manchester.

Diana van Gent
diana.vangent@cmft.nhs.uk

Goodbye

On a sad note we say goodbye to Diana in January. Diana was responsible for project management and communications at Manchester and also provided communications for both NGRLs. She is the person you probably heard from most often as she publicised work, organised training courses, developed collaborations and distributed newsletters and updates. Diana first joined NGRL Manchester in 2005 and was seconded to The Nowgen Centre for a period before returning in 2008. This was at an important period of transition as we established a new work programme, adopted new reporting requirements, recruited new staff and developed our communications strategy. Diana was key to achieving these successes and will be greatly missed, not least for her other important role in organising lab social events and for her inimitable Dutch humour. She leaves for a new post as project manager at the Centre for Research in Environmental Epidemiology (CREAL) in Barcelona: we wish her the very best for her future career and in trying to cope with the sun and an office by the beach.

Andrew Devereau
andrew.devereau@cmft.nhs.uk

Genetic information leaflets in British Sign Language (BSL): a resource for the UK genetic counselling community

Rachel Belk, Manchester

Those BSHG members with a particular interest in deafness may remember a presentation at York on the subject of improving access to genetic counselling information for Deaf people through the translation of written leaflets into British Sign Language videos available on DVDs (Belk and Trump, 2005). This project was led by Rachel Belk, a genetic counsellor in Manchester, within her specialist post that aims to improve access and communication to the service for D/deaf people (Belk, 2006).

Since then, the DVDs have been (and continue to be) freely available for copying by contacting Rachel in the Genetic Medicine department in Manchester (rachel.belk@postgrad.manchester.ac.uk). Larger numbers of copies for use with patients can also be ordered.

However, developments in video-streaming technology and broadband speeds mean that videos can now be hosted on a webpage for easy viewing. The six 'leaflets' on Recessive, Dominant and X-linked Inheritance; What is Genetic Counselling?; Genetics of Sensorineural Deafness and a Glossary of the genetic terminology used in the other leaflets can now be viewed by professionals and lay people at http://sites.mhs.manchester.ac.uk/what-is-genetic-counselling/.

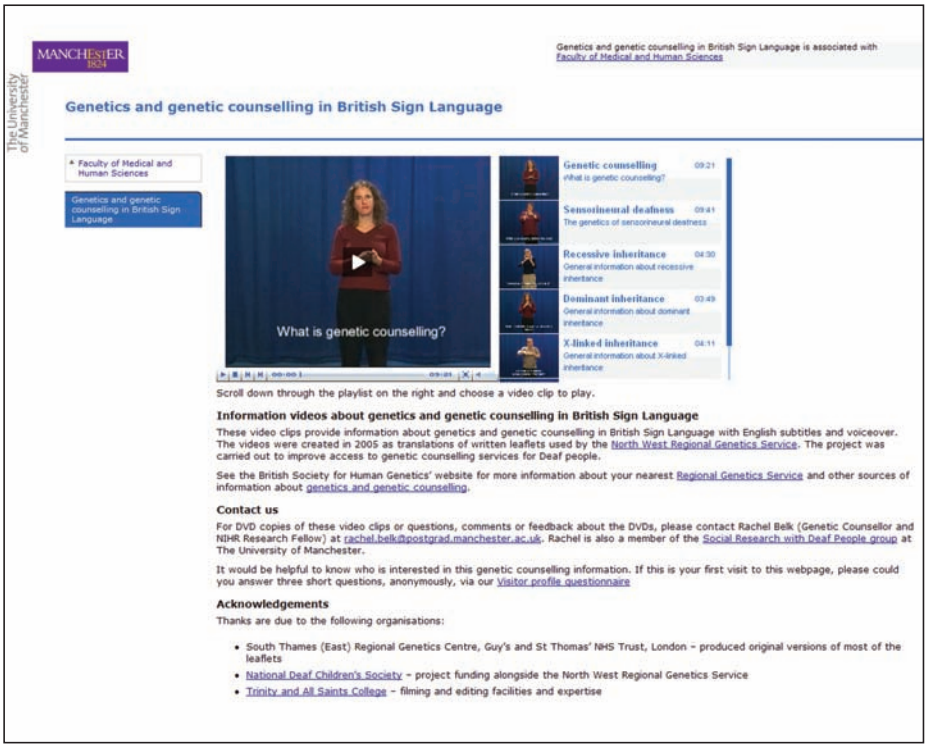
Each video has English subtitles and voiceover alongside the BSL. The page can also be accessed via the leaflets page on the Manchester Genetic Medicine website http://www.mangen.org.uk/patients/patient-leaflets.aspx

Rachel welcomes informal feedback about the content and use of the videos either by email or via the feedback option on the webpage.

References:

Belk RA. Seeing chromosomes: improving access to culturally-sensitive genetic counselling through the provision of genetic information in British Sign Language. p285-295 in D. Stephens and L. Jones.(eds) The Effects of Genetic Hearing Impairment in the Family. London, Wiley 2006.

Belk RA, Trump D. Seeing chromosomes - producing genetic information in British Sign Language. 2005 J Med Genet 42, S16. British Society of Human Genetics Conference, York.



NHS Evidence – a new information portal

William Foster, Knowledge Manager, NGEDC, Birmingham
Denise Williams, Consultant Clinical Geneticist, Birmingham Women's Hospital

In Issue 40 (January 2009) we outlined the scope and activities of the Genetic Conditions Specialist Library; part of the National Library for Health (NLH). Since that article appeared the National Library for Health has merged with the National Institute for Health and Clinical Excellence (NICE) and a new information portal NHS Evidence has been launched. Its origin can be found in Lord Darzi's report on the NHS, 'High Quality Care for All' published in June 2008 [1]. The report stated that "NICE will manage the synthesis and spread of knowledge through NHS Evidence – a new single portal through which anyone will be able to access clinical and non-clinical evidence and best practice, both what high quality care looks like and how to deliver it."

Launched in April 2009, NHS Evidence provides easy access to a comprehensive evidence base for everyone in health and social care who takes decisions about treatments or the use of resources – including clinicians, health professionals, commissioners and service managers – thus improving health and patient care. It provides access to a range of information types, including primary research literature, practical implementation tools, guidelines and policy documents. Part of its extensive resource base is the former National Library for Health and its thirty-four libraries now called specialist collections. It is a freely available service but users wishing to access external databases (which are part of the procured content of the NHS) need to login using an Athens password. NHS Evidence utilises Microsoft's FAST search software enabling filter options to be displayed allowing users to narrow searches by category of information such as: source of information, information type, clinical query, medicine and devices etc. At present the new portal overlays the former National Library for Health, so although there is a seamless link between the two, users wishing to focus exclusively on the specialist collections will detect the lack of uniformity across the old and new site pages.

A particular enhancement in Release 2 (October 2009) is My Evidence which allows users to register, create their own space and specify their particular areas of interests. Users can save the results of a search they have made; save a piece of information they have found as a result of their search; receive news feeds automatically alerting them to news about their area of interest; and receive regular updates about new information in their field of interest that has been published and which can be accessed through NHS Evidence. They can also rank individual resources according to perceived usefulness.

The challenge facing a service such as NHS Evidence is the huge range of potential information available. The 'formal evidence' is being sourced from a number of different organisations. Although the majority of this evidence is already available to the health service through various channels, one of the key benefits of NHS Evidence will be to consolidate datasets and provide access through one overarching system. In this way NICE are hopeful that currently-available evidence will be much easier to access and use. A rigorous accreditation process is in place to ensure the quality of the new service, and the first fully accredited resource providers have recently been approved. The concept of the accreditation process is based on a need to see standards of information being raised so that practitioners can have confidence in using evidence to develop health and social care services.

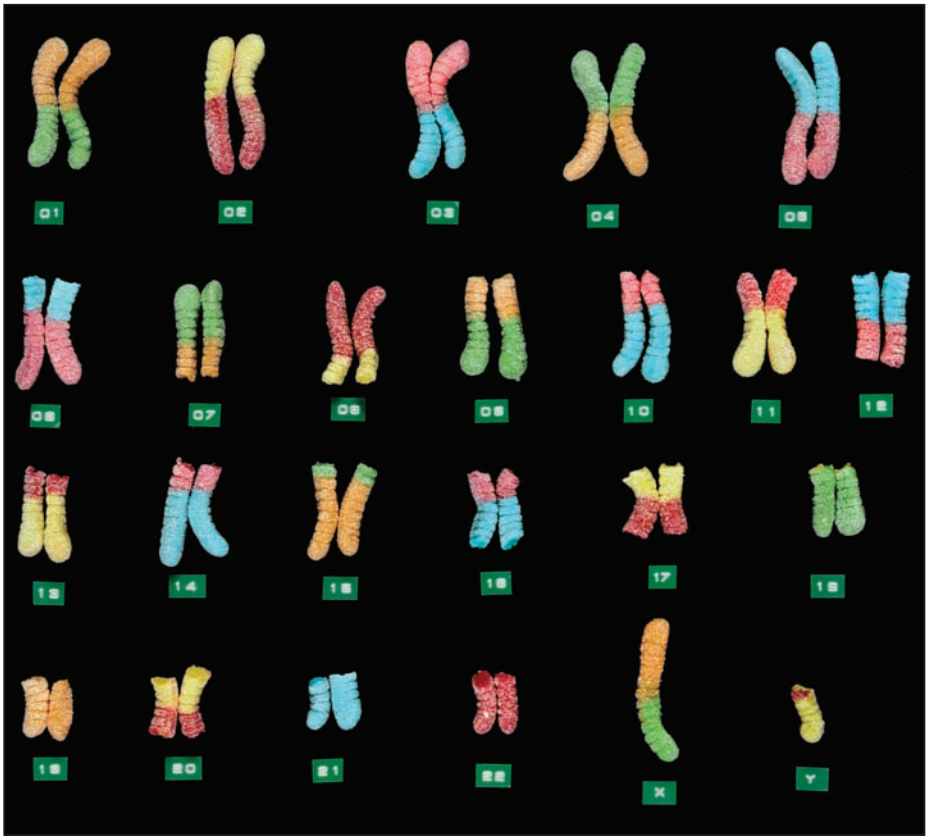
[1] Darzi A. High-quality care for all: NHS Next Stage Review final report. London: Department of Health, 2008.

NHS Evidence can be found at: www.evidence.nhs.uk If you have any comments or would like more information on The Genetic Conditions Specialist Collection please contact William Foster (0121 623 6882, william.foster@geneticseducation.nhs.uk

Chromosomes, 2005, by Kevin Van Aelst

Martin Schwarz

We've seen chromosomes made out of socks, Lego bricks and all sorts – but I had not imagined that we would find them made out of Gummi Worms. Artist Kevin Van Aelst of Connecticut has a different take on everyday items (often foodstuffs!) portraying sophisticated and complex imagery in an unconventional and sometimes light-hearted way. His 'Chromosomes, 2005' is one of many such examples that can be seen on his website (http://www.kevinvanaelst.com/art.html), including such gems as 'Cellular Mitosis (Krispy Kreme), 2005' which portrays several stages of mitosis on a Krispy Kreme donut – well, you'll have to see for yourself! Kevin describes his work as "examining the distance between the 'big picture' and the 'little things' in life" - something that should appeal to those of us who deal with chromosomes and DNA.



Oxford Ataxia Centre launch

Dr Andrea Nemeth, Oxford

A new clinical service for patients with ataxia was launched at the John Radcliffe Hospital in Oxford in December 2009. Ataxias are a heterogeneous group of neurological disorders, many of which are caused by genetic mutations, affecting speech, balance and coordination. The Oxford Ataxia Centre has been set up to offer integrated multidisciplinary care for ataxia patients. Oxford became the third specialist ataxia centre in the UK following formal accreditation by Ataxia UK, the national charity for people affected by ataxia.

Ataxia UK and Thames Valley DeNDRoN (Dementias and Neurodegenerative Diseases Research Network) are jointly funding an Ataxia research nurse to help facilitate patient involvement in research and improve patient experience through support provided. DeNDRoN is a NHS-based network dedicated to supporting research in ataxias, Huntington's disease, Parkinson's disease, motor neurone disease, and dementia.

This research nurse is part of a team working on a new study assessing the clinical features of patients with Cerebellar Ataxias, and correlating these with any genetic mutations found. The genetic analysis is funded by Ataxia UK and the Oxford Biomedical Research Centre. The project team is looking to recruit people with ataxia from across the UK for this study.

For more information, please contact Dr Andrea Nemeth, Consultant and Honorary Senior Lecturer in Clinical Genetics, on (01865) 226020, or by post: Department of Clinical Genetics, Churchill Hospital, Old Road, Headington, Oxford OX3 7LJ.

Announcements

New national specialist service for Ehlers-Danlos Sydrome

A new Ehlers-Danlos Syndrome (EDS) specialist clinic has been set up nationally (see CGS section for full article).

To make a referral
Please do not hesitate to contact us informally if you wish to enquire about whether a patient would fit the criteria for this service.

LONDON
Professor F M Pope
Ehlers-Danlos Syndrome National Diagnostic Service
NW Thames Regional Genetics Centre
Level 8V, Northwick Park & St Mark's Hospitals
Watford Road
Harrow
Middlesex HA1 3UJ

Tel: 0208 869 3166
Fax: 0208 869 3106
Email: Nlh-tr.EDSLondonOffice@nhs.net

SHEFFIELD
Dr G J Sobey
Ehlers-Danlos Syndrome National Diagnostic Service
Sheffield Clinical Genetics Department
Sheffield Children's Hospital
Western Bank
Sheffield
S10 2TH

Tel: 0114 2717764
Fax: 0114 2737467
Email: EDS@sch.nhs.uk

The Bristol Genetics Laboratory has moved

The Bristol Genetics Laboratory moved into a new Pathology Sciences building in November, designed to make it an attractive state of the art workplace for staff and to make way for further developments as part of the planned Super-Hospital at Southmead Hospital (www.superhospitalforbristol.nhs.uk).

The laboratory is situated on the 1st floor of the new building along with Biochemical Genetics. The ground floor houses a Blood Sciences automated laboratory along with laboratories for Clinical Biochemistry, Haematology and Immunology which will bring these disciplines together and facilitate closer working.

The new address is:
Bristol Genetics Laboratory
Pathology Sciences
Blood Sciences and Bristol Genetics
Southmead Hospital
Bristol
BS10 5NB

The main laboratory contact phone numbers remain the same, i.e. 0117 323 5570 / 6271. Staff Email addresses remain the same as before.

Visitors are very welcome.

Bristol Genetics Laboratory service update

We would like to inform clinicians of our most recent new services for the following:

1. DHCR7 gene sequencing for Smith-Lemli-Opitz syndrome (OMIM 270400).

2 . LITAF (SIMPLE) gene sequencing screen (OMIM 603795) for Charcot-Marie-Tooth disease type 1C (OMIM 601098).

3. For Axenfeld-Rieger syndrome (ARS) (OMIM 180500/602482): dosage analysis for FOXC1 (OMIM 601090) and PITX2 (OMIM 601542) using MLPA followed by full gene screen of FOXC1 and PITX2 by direct sequence analysis.

For more information on the above services, please contact the following via the main Genetics office on Tel: 0117 323 6271:

For DHCR7: Hilary Sawyer
Email: hilary.sawyer@nbt.nhs.uk

For LITAF and ARS: Thalia Antoniadi
Email: thalia.antoniadi@nbt.nhs.uk

Announcements cont.

New chief executive for PHG Foundation

The PHG Foundation is the working name of the Foundation for Genomics and Population Health, an independent, non-profit health service and policy development organisation based in Cambridge. In September, we were pleased to welcome Dr Mukesh Kapila CBE as our new Chief Executive. He originally trained in medicine and public health, but is best known for his work in international development and humanitarian affairs. He has held leading roles within the World Health Organization, the International Federation of Red Cross and Red Crescent Societies, the United Nations and the World Bank, as well as the UK government.

Dr Kapila is impatient to see the fruits of biomedical innovation realised in the form of interventions to meet the most pressing health needs. In line with our core aim of making science work for health, he is leading us in an expanded international remit, using genomics to deliver improved health services for vulnerable populations around the world, as well as in the UK. For example, one major new project is developing a needs assessment toolkit for low and middle-income countries to assess and plan simple, cost-effective services to improve care and reduce the incidence of birth defects, most of which have genetic causes.

Our former Executive Director, Dr Ron Zimmern, is now Chair of the PHG Foundation's Board of Directors, and is developing a portfolio of new ideas and interests in support of our mission and strategic agenda.

For further information, contact Philippa Brice: philippa.brice@phgfoundation.org.

Graham Bull Prize in Clinical Science 2010

The Royal College of Physicians is pleased to announce that the Graham Bull Prize in Clinical Science 2010 is now open for applications.

This award was established in 1988 in honour of the late Sir Graham Bull who was the first Director of the Clinical Research Centre at Northwick Park. A Trust for the Graham Bull Prize was set up to provide money for young research workers under the age of 45 who feel that they have made a major contribution to clinical science. The work can cover a wide range of expertise, such as molecular and cellular biology, imaging technology, psychiatry, or health sciences. The award is open to both clinical and basic scientists who must apply for their own work to be considered. The sum of £1000 will be awarded to the prize winner.

The closing date for applications is 31 March 2010. Please find attached a publicity leaflet giving all details of this Prize. This information is also available, along with an application form, on our website at www.rcplondon.ac.uk/trustfunds.

Spanish translator needed

At Unique, the Rare Chromosome Disorder Support Group, we now have more than 100 disorder-specific information guides available for families and professionals. The guides cover a huge variety of conditions, from the relatively common (such as 47,XYY) to the extremely rare (such as Ring 2).

A number of our guides are translated into the major languages of Europe. However, we receive a disproportionate number of requests for individual guides to be translated into Spanish – and so far, we have not sourced a Spanish translator. We do stipulate that translators are native speakers of the language they are translating into and have a background in genetics.

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

Contacts:

Prisca Middlemiss
prisca@rarechromo.org 020 8992 9933

Sarah Wynn
sarah@rarechromo.org 0203 211 1098

Announcements cont.

New Year Honours 2010 - Professor Sir John Burn

The BSHG is delighted to congratulate John Burn, Professor of Clinical Genetics at The University of Newcastle, who was awarded a knighthood for services to medicine in the New Year Honours list.

Direct Debit Subscriptions For 2010/2011

The Membership subscriptions will be collected by direct debit during April 2010 (see table below for breakdown for each constituent group).

Subscription	ACC	AGNC	BSHG only	CGS	CMGS
BSHG component	40	40	55	40	40
Payable to Constituent Society	15	20	-	25	15
TOTAL	55	60	55	65	55
Cancer Genetics Group	15	15	15	15	15
TOTAL including CGG membership	70	75	70	80	70

ESHG: For those members who have also opted to take out Affiliate Membership of the ESHG an additional fee of £32 will also be collected – please note this is a small increase of £2 from 2009/2010.

Welcome to new members

38 new members were elected to the British Society for Human Genetics in September:

Dr Kristin Marie Abbott (Human Genetics)
Dr Manir Ali (Human Genetics)
Ms Mary Anderson (Cytogenetics & Cancer Genetics)
Dr Julian Asher (Molecular Genetics)
Miss Natalie Bibb (Molecular Genetics)
Mr George Burghel (Cancer Genetics)
Dr Hakan Cangul (Molecular Genetics)
Mrs Joana Costa (Cytogenetics)
Dr David Gonzalez De Castro (Molecular Genetics & Cancer Genetics)
Mr Philip Dean (Molecular Genetics)
Dr Andrew Douglas (Clinical Genetics)
Dr Clare Drakeford (Human Genetics)
Miss Clare Durajczyk (Cytogenetics)
Mrs Julia Finch (Cytogenetics & Cancer Genetics)
Dr Rebecca Igbokwe (Clinical Genetics)
Prof Chris Inglehearn (Human Genetics)
Mrs Chidinma Kamalu (Cytogenetics)
Miss Hoda Kardooni (Molecular Genetics)
Mrs Sukhbir Kaur (Human Genetics)
Miss Verity Leach (Human Genetics)
Dr Deborah Mackay (Human Genetics)
Miss Nichola McSkelly (Cytogenetics)
Ms Bayarmaa Medley (Cytogenetics)
Dr Sadat Muzammil (Cancer Genetics)
Mrs Emma Newman (Cytogenetics)
Mrs Anna O'Grady (Molecular Genetics)
Mr Joseph Omololu-Aso (Molecular Genetics)
Dr Ann Orren (Molecular Genetics)
Miss Lara Park (Cytogenetics)
Miss Marina Parry (Cancer Genetics)
Dr Heema Patel (Molecular Genetics)
Dr Rebecca Poole (Molecular Genetics)
Mrs Sarah Rolleston (Molecular Genetics)
Mrs Susan Stewart (Cytogenetics)
Dr Helen Mary Stuart (Clinical Genetics)
Dr Julie Turbitt (Cytogenetics)
Dr Gavin Wilkie (Molecular Genetics)
Dr Brian Wilson (Clinical Genetics)

BSHG Annual General Meeting – held at 18:00 on Tuesday 1 September 2009, University of Warwick

Members were welcomed to the meeting.

Treasurer's report

Rob Elles reported the treasurer's report, which had been prepared by Peter Farndon. Mandy Barry has now taken on the task of managing the Society's budget after an interim period, which had been temporarily managed by Peter Farndon. It was reported last year that the Society was in a position where it was no longer sustaining a break even position and was eating into its reserve funds to cover costs. This was due mainly to long standing reliance on profits from the annual conference to cover the operational costs of running the Society, its administrative office and its other functions. Over the past few years the cost of running the conference have risen far more than the revenue generated and it has broken even at best for a few years now. The reserve fund for the society is now below the level required by the Charity Commission to meet all its liabilities if the Society was wound up. This situation has been addressed in a number of ways over the past year including the change of conference venue to Warwick where the venue pricing structure was much more favourable than York had become over the past few years. In addition, at the AGM in York 2008, members voted in favour or a small increase in membership fees. The newsletter editions have been reduced to twice a year and the proposed Business Manager/Chief Executive Officer post appointment has been deferred until further notice. These measures have not yet been reflected in the accounts particularly since the increased membership fee and 2009 conference income both impact after the end of the 2008/9 financial year.

The Treasurer and Auditor were clear about their concerns about financial viability and the Council discussed potential further cost saving and fund generating measures that might help the situation come back into balance. At the AGM members were asked to consider making a voluntary charitable contribution to help restore the Society's reserves (more to follow by email) and in the next few months a working party to include the BSHG Treasurer and Treasurers from the constituent and affiliated groups would review options including looking at a sliding scale of membership fees according to professional group and therefore likely income bracket.

Chair's report

The regular business of the BSHG has continued apace with highlights being the responses on behalf of the society to the House of Lords Enquiry on Genomic Medicine and the Nuffield Council for Bioethics report on direct to consumer genetic testing.

The Chairman has introduced the e-bulletin which a number of members commented was very useful – especially as it has been kept very brief and informative.

Constituent groups report to BSHG Council and highlights from their activities include

a joint meeting of Heads of Laboratory in January 2009 for the ACC and CMGS and a follow up joint meeting of executives and a planned scientific meeting with a joint day in Oxford (2010). Training is a common concern.

The CGS awarded its first international scholarship to Professor Shubha Phadke from India, the lead clinicians group continues to oversee and shape genetic service development and delivery and representatives of all the constituent groups were involved in developing the Department of Health 18 week pathway for Clinical Genetics referrals.

For the AGNC applications for registration are now considered annually with intention to submit being made in March and portfolio submission in September of the same year. The DH has agreed to part fund a further 10 trainee genetic counsellor posts in England.

The Modernising Scientific Careers initiative has generated concern. The AGNC responded to an article in the Times suggesting that Health Care Scientists would have a role in explaining test results to patients; a role filled by GCs and Clinical Geneticists. MSC is now at the pilot stage and Genetics has taken a full role in its implementation.

Affiliated Societies

The Cancer Genetics Group continue to review up-coming NICE guidance calls and lobbied for the inclusion of familial cancer patients in the scope of new breast cancer management guidelines and the new colorectal cancer management guidelines. However this was not accepted. The Winter CGG meeting is being held in November in conjunction with the annual British Association of Surgical Oncology (BASO) meeting in London.

The affiliation of the Society for Genomic Policy and Population Health (SGPPH) was voted on and agreed at the AGM this year. This group were welcomed to the BSHG as a newly affiliated society with a special interest. The group is chaired by Layla Jader and the secretary is Alison Hall.

The Cardiac Genetics Group is growing in numbers and may also seek affiliation status in the future.

Forthcoming conferences

BSHG officers

There will be changes in the Executive body of the BSHG starting with the Chairman, Rob Elles who stands down after this meeting. He will hand over to Christine Patch for the next year and continue to support the Chair for a further year as Past Chair. A new Chairman elect will be sought ready to take over when Chris has served her term of Office. The Chairman urged society members to consider volunteering for roles as they arise including next year the General Secretary role, and roles within the conference organising committees.

General Secretary's report

The membership of the Society remains healthy, is increasing despite the increase in fees and has now 2012 members. Membership of the ESHG via BSHG membership payments was taken up by 135 members of the Society.

Conference Organiser's report

The conference this year at Warwick, despite having to be positioned at the end of a bank holiday weekend attracted only 30 fewer delegates than the previous year and the costs to the society were considerably reduced so that we are anticipating a reasonable positive balance after this year. Members were strongly encouraged to complete evaluation forms so that a decision could be taken about the venue for next year.

Summarising the year

Rob Elles thanked members of the Society and the administrative office for their support and Diana Eccles thanked Rob for his work as Chair of the Society over his term of office and wished Chris Patch luck for when she takes over the role immediately after the AGM 2009.

Cancer Genetics Group joint Spring Conference with the Dutch Clinical Genetics Society : 10-11 March 2010 (Joint day 11 March 2010)

Venue: Artis Royal Zoo, Amsterdam
Contact: Mrs Tine Verheij-van Der Linden, Bureau Routine, Congress Office, PO Box 31249, 6503 CE Nijmegen, The Netherlands.
Email: info@routine-nijmegen.nl

Clinical Genetics Society joint Spring Conference with the Dutch Clinical Genetics Society : 11-12 March 2010 (Joint day 11 March 2010)

Venue: Artis Royal Zoo, Amsterdam
Contact: Mrs Tine Verheij-van Der Linden, Bureau Routine, Congress Office, PO Box 31249, 6503 CE Nijmegen, The Netherlands. E: info@routine-nijmegen.nl

Association for Clinical Cytogenetics Spring Conference : 12-14 April 2010 (joint day 14 April with CMGS)

Venue: Keeble College, Oxford
Contact: cytogenetics@orh.nhs.uk
website:
www.springmeeting.cytogenetics.org.uk

Clinical Molecular Genetics Society Spring Conference : 12-14 April 2010 (joint day 14 April with ACC)

Venue: St Catherine's College, Oxford (www.stcatz.ox.ac.uk)
Contact: cmgs2010@orh.nhs.uk
Please Note that the joint day on 14 April is also at St Catherine's College

Bioinformatics for Clinical Geneticists: 22 – 23 April 2010

Venue: Nowgen, The Nowgen Centre, 29 Grafton Street, Manchester M13 9WU
Cost: £200.00
Contact: Dr Angela Davies Tel: 0161 276 3200, email: angela.davies2@cmft.nhs.uk

Association of Genetic Nurses and Counsellors Spring Conference : 29 April 2010

Venue: St George's Hospital, London
Contact:
vishakha.tripathi@stgeorges.nhs.uk
jennifer.wiggins@rmh.nhs.uk

Bioinformatics for Cytogeneticists and Molecular Geneticists: 6 – 7 May 2010

Venue: Nowgen, The Nowgen Centre, 29 Grafton Street, Manchester M13 9WU
Cost: £200.00
Contact: Dr Angela Davies Tel: 0161 276 3200, email: angela.davies2@cmft.nhs.uk

European Society of Human Genetics Conference : 12-15 June 2010

Venue: Gothenburg, Sweden
Contact: Please consult the website – https://www.eshg.org/

Is Medical Ethics Really in the Best Interest of the Patient? 14-16 June 2010

Venue: Uppsala Concert and Congress Hall, Sweden
There is an open call for papers - deadline 15th February 2010.
Website:
http://medical-ethics2010.crb.uu.se

British Human Genetics Conference: 6-8 September 2010

Venue: University of Warwick
Contact: Ruth Cole (bhgc@bshg.org.uk)
website: www.bshg.org.uk

Conference reports

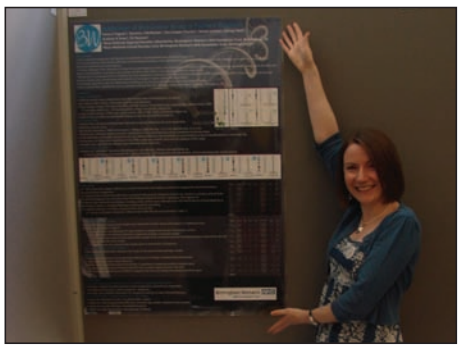
European Cytogenetics Conference - Stockholm, Sweden, July 2009

Fiona Sara Togneri, West Midlands Regional Genetics Laboratory, Birmingham

On 3 July 2009 I travelled to Stockholm in Sweden for the 7th European Cytogenetics Conference. Home of the Nobel Prize, Stockholm provided an ideal location for this meeting of Cytogeneticists from across the globe.

ArrayCGH played a central role in discussions of clinical cytogenetics and results were presented from many extensive array studies. New syndromes (including microdeletions of 17q23 and 1q41q42) were proposed and a shift in preference from BACs to higher resolution array platforms was difficult to ignore.

A working party meeting on prenatal arrayCGH was also of great personal interest. It provided an ideal opportunity for scientists from diagnostic centres across Europe to learn from each other's experiences and to discuss the future of this exciting area of development.



This was my first international conference and I felt privileged to have my work presented in the same setting as so many noted scientists. I would like to take this opportunity to thank the BSHG and my own laboratory for their support in helping me attend this engaging conference.

European Cytogenetics Conference - Stockholm, Sweden, July 2009

Kalliroi Stergianou, Cytogenetics Dept, Nottingham University Hospitals

I was fortunate to attend the extremely successful 7th European Cytogenetic Association (ECA) conference (attended by 850 scientists), hold in the City Conference Centre in Stockholm. The ECA conferences take place every two years and it is an event that brings cytogeneticists from the whole Europe to share their knowledge and views.

The presentations reflected the evolution of Cytogenetics to Cytogenomics and the highlight was the rapidly expanding field of human variation which influences susceptibility to disease.

A special session on Darwin in the 21st century marked the 200th anniversary of the birth of Charles Darwin and highlighted the relevance of his work to current biology.

The program included several concurrent Permanent Working Group Reports, satellite workshops and poster exhibitions which leave you with frustration of being unable to attend all the sessions. Several concurrent satellite symposia were hold during lunch time from Abbott, PerkinElmer, Agilent, Cartagenia and Affymetix.

American Society of Human Genetics meeting 2009

Aloha! This year's ASHG meeting was held at the Hawai'i convention centre, close to Waikiki beach on the Pacific island of O'ahu. After 14 years in post it seemed time to experience an ASHG meeting and the location did not disappoint; amazing scenery, a balmy climate and convivial atmosphere.

Next generation sequencing was the focus of many orals, posters, exhibitions and also the theme of the excellent Human Genome Variation Society satellite meeting. We heard the first successful example of exome sequencing to identify the cause of a mendelian disorder (Miller syndrome reported by Ng et al 2009, Nature Genetics Advance Online Publication doi:10.1038/ng.499). Elaine Mardis' group brought us the first acute myeloid leukaemia genome sequence and have now sequenced both a primary breast tumour and its metastatic brain tumour. Gil McVean gave an update on the 1000 genomes project, but according to Evan Eichler the 1000 refers to the number of people involved in the project rather than the genomes sequenced!

The Exeter Complex Traits group took to the podium for the Genetics of Size, Shape and Sugar GWAS session co-moderated by Tim Frayling with presentations from Rachel Freathy (birth weight), Hana Lango Allen (height) and Anna Murray (puberty onset). A special session to celebrate the achievements of Professor Newton Morton in his 80th birthday year highlighted the enormous progress in the field of genetic epidemiology. The new sequencing technology promises a new pace for genetic discovery and I certainly don't plan to wait so long until my next ASHG meeting.

Mapping the Genomic Era: Measurements and Meanings

Susan Kelly, Christine Knight, Claire Packman, Dave Stevens and Flo Ticehurst

Conference reports cont.

The ESRC Genomics Network (EGN) Conference 2009 in Cardiff was organised around the theme: Mapping the Genomic Era: Measurements and Meanings. The conference brought together social and natural scientists with policy makers and commentators from across the globe. It was organised by the ESRC Centre for Economic and Social Aspects of Genomics (CESAGen), a collaboration between the Universities of Cardiff and Lancaster.

Over the course of three days, delegates were treated to an impressive line up of keynote speakers from across the world.

Professor Doug Turnbull, Professor of Neurology, Newcastle University and the NCG Service for Rare Mitochondrial Disorders of Adults and Children, spoke about Mitochondrial genetics - inheritance and disease, giving a very clear and informative background to the science of mitochondrial DNA and the clinical challenges of mitochondrial disorders.

Explaining that mtDNA goes through a bottleneck very early in a female's development as the primordial germ cells develop, he described how a woman with a heteroplasmic mutation may therefore have children with widely different levels of mutation. As he pointed out, providing counselling for women with mtDNA mutations is complicated. Later in his lecture, Professor Turnbull described how many new techniques are being considered to help prevent transmission of mtDNA mutations. As he pointed out though, such efforts raise many ethical questions.

One workshop focussed on non-invasive prenatal diagnosis, it was convened by Dr Susan Kelly and Dr Hannah Farrimond who are involved in research in this area at Egenis, Exeter University.

Dr Kelly presented a brief technical background to current and imminent non-invasive prenatal testing technologies and their clinical introduction before posing the question: "What should the ethical, social and policy response be to the clinical introduction of non-invasive prenatal testing?"

Following contributions from panelists Dr Annie Procter (All Wales Medical Genetics Service), Dr Ainsley Newson (University of Bristol), Dr Adam Bostanci (Hughes Hall, Cambridge), the debate focused on informed consent, what that might mean in practice, and whether counselling would be adequate.

A policy engagement plenary session was organised in collaboration with the Society for Genomics Policy and Population Health. This session provided the opportunity for delegates to engage in dialogue with those with interests in the public health implications of genomic medicine. The session was chaired by Dr Layla Jadar, President of SGPPH.

Speakers were Dr Jane Wilkinson (Deputy Chief Medical Officer for Wales), Dr Berwyn Clarke, (Chief Scientific and Development Officer for Lab21), and Alison Hall (Foundation for Genomics and Population Health). Their presentations sparked questions and discussion on the role of genetic factors in adverse drug reactions, the resource implications of using genomics in public health, discrepancies between Welsh and national provision in genetic services, and the need to guard against genetic exceptionalism and also ensure privacy and data security in the context of public health genomics.

A full report of the conference is available through the EGN's website, please visit www.genomicsnetwork.ac.uk or contact Flo Ticehurst, Cesagen, ticehurstf@cf.ac.uk, 029 2087 0024.

The EGN's next conference is organized by ERSC Genomics Forum in partnership with the OECD Global Forum on Biotechnology and will take place in Paris, contact the ESRC Genomics Forum on 0131 651 4747 for further details.

The Macular Meeting, Moorfields Eye Hospital (MEH), 14 Oct 2009

Sharola Dharmaraj (MEH) and Darren Fowler (Southampton University Hospitals NHS Trust)

A fantastic meeting to attend for all those BSHG readers interested in eyes and genes. One day was particularly devoted to age-related macular degeneration (ARMD). The genetics of ARMD has become better understood and therapy is now a clinical reality especially for patients with the exudative form who benefit from intra-ocular injections of anti-angiogenic factors. It is estimated that about 25% of people over the age of 60 in the UK have some degree of vision loss caused by the pigment epithelial degeneration and the impact of central visual loss from severe AMD in the aging population has an enormous socio-economic consequences. Following retinal pigment epithelial (RPE) loss, the photoreceptors degenerate, and the primary aim in macular degeneration is to replace the diseased support cells (RPE) with cells derived from human embryonic stem cells, which can then be transform into photoreceptors (primarily cones and rods).

Andrew Webster who introduced the topic with the concept of AMD as a multifactorial genetic disease discussed the role of

Conference reports cont.

complement dysregulation, susceptibility loci, and association studies.

Tony Moore presented some interesting case studies of children with inherited retinal dystrophies and it is one such disorder, Leber congenital amaurosis (RPE-related LCA) that has recently been treated using ocular gene therapy. There was some discussion about foveal aplasia seen in albinism and in aniridia (a developmental abnormality involving FOXC2) leading to pan ocular disease.

North Carolina macular dystrophy (OMIM 136550, autosomal dominant inheritance, gene not identified) is thought to have originated from a Northern Irish family who migrated to America and involves failure of development of the macula. Linkage analysis of affected family members maps the disease to 6q14-16 (MCDR1) and interestingly there are a number of other similar diseases mapping to the same locus such as autosomal dominant drusen with macular degeneration, Stargardt-like macular dystrophy (OMIM 600110, autosomal dominant, STGD3) and autosomal dominant atrophic macular degeneration. Progressive bifocal chorioretinal atrophy (OMIM 600790, gene not identified) is also linked to 6q14-16 and Leber congenital amaurosis caused by mutations in lebercilin map to the same area.

Nine years after the draft Human Genome was completed (2000) there are still diseases with genes unidentified.

The September 2009 issue (20) of Current Opinions in Ophthalmology is devoted to 'Ocular Genetics' (Editor Allen C Ho), and provides insights into the ever widening field of eyes and genes.

Travel awards

How to apply for Travel Awards

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

It is highly unlikely that retrospective awards will be given.

Applications should be sent to Mrs Ruth Cole, the Society's Administrator in Birmingham. There is no set form but please give as much information as possible and if you have submitted or had an abstract accepted please enclose a copy (it will be treated in strict confidence) indicating whether it is spoken or poster.

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

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

1 January	1 April
1 July	1 October

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

Electronic Mailing

Following on from the success of the e-bulletin and in view of the Society's financial situation with the need to make savings, we will in future be sending out most information to all members electronically. From 2010 this will include all the information for the British Human Genetics Conference and the BSHG newsletter; from 2011 all the information regarding the Spring Conferences.

We realise that this will be a big change in the way information is disseminated to Members but feel that it is the way forward.

With that in mind, may I ask everyone to please ensure that we have your up to date email address and that you will keep us informed of any changes.

BSHG News Editors

Deadline for contributions for next issue is 30 April 2010

BSHG Editor: Dr Helen Middleton-Price
BSHG Executive Officer: Mrs Ruth Cole

Nowgen - A Centre for Genetics in Healthcare, The Nowgen Centre, 29 Grafton Street, Manchester M13 9WU

Tel: 0161 276 6095
Fax: 0161 276 4058
Email: helen.middleton-price@cmft.nhs.uk

Editorial

May I take this opportunity to wish all of you a happy and successful New Year! Hopefully you all had a nice relaxing Christmas too.

In this edition we have a plethora of articles for you to read during your coffee breaks in the lab. We have three interesting articles from the last round of ACC research grant award winners: one from the Edinburgh laboratory on the use of microarrays in the investigation of gliomas, one from Liverpool on microarrays in the investigation of uveal melanoma and the final article from the Cambridge laboratory on FISH investigations in cervical cancer.

We have a report on the 7th European Cytogenetics conference in Stockholm. I would remind you all at this stage that if you would like to present your work at an exotic conference location, you can apply for an ACC travel award. Details are on the ACC website but applications must be made two weeks before an ACC council meeting which are usually held on the first Tuesday in March, June, September and December, for full details contact the treasurer.

There are two articles from the National Down Syndrome Cytogenetic Register; the first on the vast reduction in prenatal tests between 2000 and 2008 and the second on the trends in antenatal diagnoses and live births with Down syndrome in England and Wales.

We have an account from Mark Sales on his swim across the Channel for charity and a fitting tribute to Rob Morgan, who sadly passed away last year and is missed by his colleagues in Leeds and others from within the profession.

In an effort to reflect the changing membership of our profession, we have an article on a Genetic Technologist (GT) study day held in Birmingham. Hopefully we can continue this in future editions of the newsletter by having articles of interest to GTs.

Lastly, don't forget that our annual conference this year will be hosted by the Oxford laboratory. Hopefully they have been inundated with submissions of abstracts for presentation at the meeting. Details can be found on the conference website.

Many thanks to all of you who contributed articles to this edition of the newsletter!

Simon

Array Comparative Genomic Hybridisation (array-CGH) assessment of 1p 19q status on archived paraffin embedded samples

Freddie H Sharkey1*, Fiona Bergin1, James Iremonger1, Eddy Maher1, Colin Smith2, 3

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Assessment of 1p19q deletion status is routinely undertaken in many centres when reporting oligodendrogliomas, or gliomas with an oligodendroglial component. This co-deletion has been described in between 60-80% of such cases and is associated with a good response to chemotherapy and ultimately prolonged patient survival. There are a range of tests currently available for this assessment, with loss of heterozygosity (LOH) PCR the most commonly used. In addition to being able to readily assess 1p and 19q imbalances, array-CGH is a technique which enables whole genome profiling and is capable of identifying cryptic and unidentified prognostic and diagnostic genetic markers in this cohort. In Scotland, guidelines published through the Scottish Adult Neuro-Oncology Network (SANON) have, as a stated goal, that all gliomas with an oligodendroglial component will have 1p 19q assessment (www.neurooncology.scot.nhs.uk/health_professionals/standards.aspx). Our laboratory has previous experience with both LOH PCR studies and with FISH, and we are aware of the strengths and limitations of these techniques for detection of the 1p19q signature co-deletion. Typically array-CGH is undertaken on frozen tissue or blood samples, to provide optimal DNA quality for genomic copy number assessment. However, most neuropathology archives are formalin fixed paraffin embedded (FFPE) tissue blocks and occasionally some current specimens will arrive in the neuropathology laboratory already in formalin. This study was designed to look at the feasibility of array-CGH using FFPE blocks. In total 38 cases (32 FFPE / 6 frozen tissue) were identified from the archive of the Department of Neuropathology, Edinburgh and consisted of 14 oligodendrogliomas WHO grade II, 15 anaplastic oligodendrogliomas WHO grade III and 9 glioblastomas. FFPE tissue blocks were selected with maximal quantities of tumour wherever possible.

FFPE samples are a desirable source of archival material for both copy number imbalance and gene expression profiling studies due to their availability and the possibility of retrospective studies. Extracted DNA from this material is often heavily cross-linked, heterogeneous (i.e. mix of cells of different genomic composition), substantially fragmented, and rarely composed of 100% tumour DNA. As such many molecular genetic approaches are fraught with difficulties that accompany FFPE extracted material. The current study represents one of the first applications of oligonucleotide array-CGH for whole genome profiling of archived FFPE gliomas. The initial objective for this project was to successfully establish a rapid and readily reproducible array-CGH protocol that could be used as a routine diagnostic assay using DNA extracted from 6 frozen glioma tissue biopsies. If successful, it was anticipated that array-CGH could then be applied for copy number analysis of a further 32 FFPE glioma specimens using a 44K oligo array to determine the frequency of additional copy number imbalances.

A paired DNA sample approach, using a single case where DNA was extracted from both frozen tissue and FFPE material was used as a correlative measure of experimental noise. This was intended to enable a rapid comparative analysis of glioma DNA performance using the same case that was isolated from both frozen tissue and FFPE. Significantly, all copy number aberrations could easily be identified by BAC array-CGH from both DNA sources. Due to the much fragmented nature of many FFPE DNAs, the shorter length of the DNA probes (60mers) on the oligo array (as opposed to BACs ~70Kb -250Kb) was expected to improve the interpretation and analysis by reducing experimental noise. The use of an array with 44K probes also offers better resolution (backbone resolution of ~70Kb) for identifying new novel genetic markers in such cases. The ultimate expectation was that all archival glioma material available in Edinburgh could be screened for microscopic and submicroscopic imbalances with the view that novel markers could be identified.

The 1p19q co-deletion was detected in 85% of the oligodendroglial tumours examined, which generally concurs with data documented in the literature. The highest frequency aberrations identified in the oligodendrial cohort involved deletions of chromosomes 18 (30%) and 4 (25%). In total, 80% of the Grade II oligodendroglial tumours analysed displayed the deletion of 1p19q. Common copy number aberrations included deletion of 15q (30%) and loss of whole chromosome 18 (20%). Common copy number changes included deletions of chromosomes 4 (38%), 15 (23%) and 18 (38%), in addition to gains of chromosomes 11 (23%) and 7 (15%). The short arm of chromosome 9 was deleted in 2 cases, and chromosome 9 in an additional 2 tumours. Gains within chromosome 11, 16p and 19p were also commonly noted.

In contrast to the oligodendrogliomas, the 1p19q deletion was not detected in any of the 9 glioblastoma samples tested.

Common copy number changes included duplications on chromosome 7 and the short arm of chromosome 16. Deletions of chromosome 10 were noted in over a third of the tumours analysed. Moreover, duplication of the short arm of chromosome 19 was found in 55% of the glioblastoma cases analysed. A number of abnormal regions suggestive of mosaicism were identified from numerous array-CGH profiles but it was not possible to validate or quantify this data.

A major challenge is inevitably the medical interpretation of such data with respect to the gross nature of many these copy number aberrations. For example, approximately 20% of aberrations identified in this project involved entire chromosomes, with a further 20% involving specific chromosomal arms. Thus, although the ideal approach would be to identify significant candidate genes within the commonly occurring aberrations, the huge number of oncogenes and tumour suppressor genes within many of these regions makes this very unlikely. Thus it is highly probable that genomic regions of abnormal copy number, which are present at such significant frequencies, would ultimately prove to have significant consequences for the respective patients. However, it is important to state it is difficult to determine if these changes represent pathogenic imbalances at this stage or have prognostic significance. This is especially true for the subgroup of patients in which the 1p19q co-deletion is not detected, and therefore the need for additional prognostic genomic markers would be of particular benefit. Our results suggest that this is true for approximately 15% of our cohort, and this figure is reflected in the literature. Interestingly, it would seem that there is an emerging professional consensus which believes a clinical diagnosis of an oligodendroglioma tumour should be made purely on the presence of this genetic signature. It has been proposed that histology should retain a role in achieving a diagnosis of a glial tumour based on the presence of both necrosis and increased mitotic activity. However further characterisation of oligodendroglial tumours would be made using accurate and sensitive molecular genetic assays. Ultimately, this may lead to the re-classification of tumours which appear to be of oligodendroglial differentiation based on histology, but do not display the 1p19q co-deletion. Moreover, genomic typing would also eliminate any intra-observer variability that can currently exist when a diagnosis is achieved on the basis of qualitative observations.

The use of array CGH for the detection of copy number changes in patients with Uveal Melanoma

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Uveal Melanoma (UM) is the most common intraocular tumour in Caucasian adults with an occurrence rate of approximately six per million per year. The long term prognosis for all UM patients is poor with a 15 year survival rate of approximately 50%. This is because fifty percent of patients go on to produce metastases which become unresponsive to chemotherapy, with a median survival after detection of 12.5 months. The loss of chromosome 3 is strongly associated with metastatic development and is believed to be an early event in UM tumour development. There are also other chromosomal markers that are believed to be secondary to monosomy 3, including loss of 1p and gain of 8q which are associated with a worse prognosis. There is an alternative prognostic pathway for UM patients which is gain of chromosome 6 that almost always occurs in the presence of two copies of chromosome 3 and rarely undergoes metastases.

The Merseyside and Cheshire Genetics Laboratory have been working with the Liverpool Ocular Oncology Centre since 1999 offering cytogenetic analysis to UM patients. In 2007 a multiplex ligation-dependent probe amplification (MLPA) service was introduced using a specialist kit from MRC Holland which contains 31 probes that cover chromosomes 1p, 3, 6p and 8q, This approach is, however, limited to investigating specific loci. In this project microarray comparative genome hybridisation (CGH) investigations were performed on a BAC clone platform using a specialist Focus Haematology Chip (BlueGnome Ltd) with a backbone resolution smoothed to 5Mb. The aim of this project was to further characterise chromosomal aberrations common to UM and to identify novel recurrent copy number changes in the rest of the genome. Additionally, tiling FISH probes were applied for fine mapping of breakpoints of common regions of copy number change (CRC).

Thirty-two cases were obtained from patients seen at the Liverpool Ocular Oncology Centre between 2007 and 2008. All cases prior to this project had undergone MLPA analysis. The material collected was from a mixture of biopsies and enucleations, all being fresh at the time of receipt. DNA was extracted by the Molecular Genetics Department using a Qiagen Bio Robot EZ1 following the standard laboratory protocol.

Microarray CGH produced successful data for all 32 cases analysed. The mean number of chromosomal changes present throughout the genome was 5.88 with the lowest being 1 aberration and the highest being 16. The most commonly occurring aberration was gain of 6p in 68.8% of cases, with the gain of 8q being the second most common aberration in 62.5% of cases. In addition,100% of disomy 3 cases and interestingly 58.8% of monosomy 3 cases had gain of 6p. The most common copy number change seen other than 1, 3, 6 or 8 was loss of 16q in 21.9% of cases.

When looking at the data produced from this study's cohort, 12 of the 22 cases that had monosomy 3 or partial deletions of 3 had gain of 6p. Seven of these cases had i(6p), as well as high levels of aneuploidy in the genome (with a mean of 9.4 aberrations per case) and i(8q), 5/7 also had loss of 1p. Interestingly, 100% of disomy 3 cases had gain of 6p and none had loss of 6q, also the overall levels of aneuploidy in the genome were much lower with a mean of 3.4 aberrations per case.

Monosomy 3 tumours appeared to be associated with a larger amount of copy number imbalance and the presence of isochromosomes, whereas disomy 3 tumours appeared to be associated with a lower level of aneuploidy and no isochromosomes. This fundamental difference in copy number between the two pathways will have an influence on the prognosis of these two pathways. It is known that aneuploidy destabilises the synthesis, segregation and repair of chromosomes, therefore because monosomy 3 is associated with a higher level of aneuploidy, it explains why this pathway is more likely to produce these cancer specific rearrangements and therefore go on to metastasise.

Another aim of this project was to determine common regions of copy number change (CRC) in order to identify chromosomal regions harbouring possible oncogenes/ tumour suppressor genes. Chromosome 1 had the smallest CRC with breakpoints at 1p34.3-1p36.22 spanning 25.9-28.3Mb. Loss of 1p has a strong association to the monosomy 3 pathway and therefore makes it a target for further investigation for CRC that contain tumour suppressor genes or metastatic inducible genes. To further define the breakpoints, FISH tiling probes were hybridised to 4µm thick paraffin embedded tissue sections (PETS). Four tiling probes were selected for the 1p36.22 breakpoint and 1 tiling probe, RP5-983H21, was selected for the 1p34.3 breakpoint. To date, 524 genes have been identified within the minimum CRC, 1p34.3p36.22. Of these 524 genes,

17 are of particular interest, including 8 genes that have been implicated in tumour progression, including APITD1, UBE4B and NBL1 all of which are possible tumour suppressor genes in neuroblastoma. The remaining 9 genes are all involved in the cell cycle, including ZBTB17 and CDC42 that are involved in cell cycle regulation and TNFRSF8 that is a positive regulator of apoptosis.

Overall, the microarray CGH data agreed with the previous MLPA data. However in 9 cases there was some discrepancy between the two sets of data, the majority of which was due to probe positioning and data interpretation. One case did produce unexpected results because MLPA produced equivocal results for chromosomes 3 and 8 and could not determine copy number. This case was subsequently analysed by array CGH because the patient had since died from metastatic disease, which is associated with monosomy 3. Upon analysis of the array data mosaic monosomy 3 was detected. There also appeared to be a very low level mosaic gain of 8q, which would explain the equivocal results for MLPA. This case supports the use of such methodologies demonstrating that abnormal cell lines can be detected to levels as low as 10% mosaicism.

The findings of the array CGH data both supports and validates the use of MLPA for UM diagnosis as it is a sensitive technology that can detect mosaic cell lines and large regions of copy number change present in tumour samples. It is, however, the small collection of cases with unusual patterns of copy number change or with smaller regions involved that would benefit from the repositioning and addition of a small number of probes. Updating the MLPA kit by adding extra probes and therefore providing an improved coverage would allow additional information that may enable cases with unusual patterns of deletion to be better characterised.

In assessing the potential of BAC microarray technology for future tumour work, this project produced successful data on all cases analysed without the need to initially culture cells and was robust enough to allow solid tumours to be processed as single sub arrays thus reducing costs.

UM have two distinct prognostic pathways with significantly different survival rates for patients. Therefore it is imperative that all available information is collated to enable the clinicians to make an accurate, informed prognosis. Within this cohort there appears to be a strong association for large basal tumour diameter, monosomy 3, and high levels of aneuploidy which is suggestive of more aggressive tumours. The association of these factors can further strengthen the confidence of a clinician to accurately provide a prognosis and thus manage a patient's treatment more appropriately.

A full report will be presented at the ACC Spring Conference in Oxford. We would like thank the ACC Research Project Award for funding and supporting this project.

Detecting gains of chromosome 3q: A prospective study using FISH and liquid-based cytology as a predictive test for colposcopy referral

Frankie Shaw, Cambridge

Cancer of the uterine cervix is the second most common malignant tumour diagnosed in women. It is a progressive disease of the epithelial cells at the neck of the uterus caused by infection and persistence of oncogenic strains of Human Papilloma Virus (HPV). HPV can be identified in all cases of cervical cancer but not all HPV infections progress to cancer suggesting that other factors and genetic mechanisms are involved.

Cervical cancer is fatal if undetected and untreated but is a wholly preventable disease. Cervical screening programmes have reduced incidence of cervical cancer and mortality rates by 75% in industrialised countries. Cervical screening involves microscopic examination of Papanicalaou (Pap) samples or samples prepared by liquid based cytology (LBC). Introduction of LBC for sample collection and preparation has resulted in higher disease detection, fewer false-positive/negative results, and fewer recalls requiring a repeat sample collection. The advantages of LBC over the Pap smear are immediate preservation of 100% of the cell sample that can generate up to five additional slides. Cleaner and thinner cell preparations on the slides are ideal for adjunct testing and the diagnostic slide is therefore preserved.

Previous retrospective studies concluded that gain of the long arm of chromosome 3 (3q+) is a mandatory precursor to invasive carcinoma of the cervix. They also reported 3q+ in 33% of cytologically normal Pap smears in women who later progressed to cervical intra-epithelial neoplasia 3 (CIN) or invasive cervical cancer. On the other hand, about 70% of cytologically abnormal samples that were negative for 3q+ eventually regressed to a normal smear. The researchers were able to predict progression in 100% of cases and regression in 70%. However, sample sizes in most published studies were too small to provide sufficient evidence for incorporating 3q FISH testing as part of the screening programmes.

On average 1.8% of cytology investigations yield a result of mild dyskaryosis (MD) and it is estimated that about 30-35% of cases presenting with MD will progress to higher grade lesions. The stratification of first time MD cases to those likely to progress and those likely to regress would help to manage patient referrals for invasive colposcopy. Our study aims were to determine if 3q+ gain as detected by FISH on additional LBC slides could effectively identify those cases with MD who would benefit from a prompt referral to colposcopy rather than wait for the results of a 6-month follow up cytological investigation.

The study was designed in collaboration with the Cytology laboratory at Addenbrookes Hospital on 108 consecutive cases with first time MD diagnosis. Standard FISH was performed on pepsin pre-treated LBC slides with probes designed to target the TERC gene at 3q26 chromosomal region from Kreatech and mixed with control probes to identify ploidy of analysed cells. The FISH analysis on all available nuclei was performed blind by two analysts and all nuclei with 3q+ were photographed. The FISH results were categorised as abnormal (progressers) if 3 or more 3q+ (without ploidy changes) were identified per slide and normal (regressers) if there were less than 3 abnormal cells per slide. Concordant results between observers 1 and 2 were achieved on 65.1 % of cases; 29% of cases were assigned as progressers and 71% as regressers.

In our region, all cases with the first time MD result from cytology are recalled after six months for repeat cytological examination. The follow up cytology results were made available to us to determine what proportion of cases assigned as abnormal by FISH had a second abnormal cytology result and subsequent abnormal colposcopy result. Of 108 FISH analysed cases only 76 had 6-month cytology results, of these 48 samples were cytologically negative (regressers) and 28 were positive (progressers).

FISH correctly predicted 10/28 cytologically abnormal cases (35.7%) as requiring colposcopy referral 6 months earlier. Five of these FISH predicted cases were subsequently diagnosed with CIN1 or higher by colposcopy. The remaining five FISH identified cases did not have a biopsy or were negative on biopsy and will be reviewed in 6 months. Of the 28 cytologically abnormal cases, CIN1 or higher was found in 10 cases on the biopsy results, half of which were also identified by abnormal FISH. Furthermore, FISH identified 15/48 (31.3%) mild dyskaryosis cases as progressers that were diagnosed as regressers on 6-month cytology. All of the patients will be followed for an additional 6-12 months to determine if the FISH test has any predictive value.

Several limitations of our pilot study were identified. The signal intensities for 3q and control probes varied across the samples and were subject to fading, thus contributing significantly to the variation in

FISH signal scoring and interpretation between the two analysts. The LBC slides analysed by FISH were not the same slides analysed cytologically which could also have contributed to the discordance rates between the two tests. We assumed that the cytology results reflected "true" diagnosis despite known false positive/negative rates associated with this test. Furthermore, we were not able to compare the FISH results with colposcopy results after first time diagnosis. And finally, none of our samples were tested for high risk HPV. HPV testing is still being evaluated by the screening program but preliminary results showed that it can prove useful in eliminating those women who are HPV negative and at very low risk of cervical cancer.

Because of the sheer number of samples received for cervical screening and those subsequently referred for invasive testing, the additional diagnostic tests would be useful in the cervical screening program to better stratify high and low risk patients. The false positive and negative rates associated with 3q FISH testing could not have been evaluated in this pilot study due to the limitations listed above. However, FISH for 3q+ in our hands correctly predicted disease progression in half of the cases which subsequently were found to have abnormal colposcopy results. All those patients could have had colposcopy six months earlier. On the other hand, several samples with significant number of 3q+ positive cells were identified which have not been assigned as abnormal by cytology at 6-month recall and it would be prudent to follow these cases at a later date.

In conclusion, unless better and cheaper biomarkers of cervical cancer progression are identified, 3q FISH testing remains the best candidate for stratifying patients for colposcopy referrals. Long-term multidisciplinary studies are needed to assess the true predictive value of this test in a diagnostic setting.

We would like to thank the ACC Council Committee for granting us the funds to conduct our study.

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European Cytogeneticists Association (ECA) 7th European cytogenetics conference, Stockholm, Sweden July 4-7 2009

Louise Monkman, Glasgow

We arrived in Stockholm on a sunny Friday afternoon and made the short journey from the airport to our hotel. Our luggage made it along with us (courtesy of good old BA) although it later transpired that not all of our fellow delegates were so lucky.

After settling in, we headed out into the city to get our bearings and have dinner. Stockholm is a picturesque city with lots of restaurants and shops, a rather large proportion of which are H&M (don't ever arrange to meet someone "on the corner at H&M", there's one on nearly every corner in Stockholm!).

On Saturday, we found our way to the City Conference Centre and got our registration packs. We met up with colleagues from other UK labs and heard the first instalment of the lost luggage saga. I had arrived in Stockholm to present a poster and a talk, relatively unprepared and relatively unconcerned. That is until I read the conference program and saw names like Felix Mitelman, Albert Schinzel and Malcolm Ferguson-Smith in there along with mine and then a cold fear set in. I headed up to the room where my presentation at the Genetix satellite symposium was to be, finally scared into doing a bit of practice and wanting to have a quick run through my talk to check that I knew how all of the computer equipment worked. Unfortunately it didn't. I would have to switch applications to play a video partway through the talk. This shouldn't be difficult but when you have several hundred people watching you and it's an unfamiliar computer, it doesn't seem so easy.

That afternoon was filled with meetings of permanent working groups which included an interesting talk by Thomas Liehr about marker chromosomes and the database (http://www.med.uni-jena.de/fish/sSMC/00START.htm) that he maintains to further characterise the markers and their clinical phenotypes. John Barber then told us about the progress being made on the ECARUCA database (http://agserver01.azn.nl:8080/ecaruca/ecaruca.jsp) and plans for the future.

Five o'clock soon came around and I got ready to go on stage. The weather, which up until then had been bright and sunny, suddenly changed – the rain poured down and there was an ominous roll of thunder. Some people mention having butterflies before a presentation; I had a five month old baby who chose that moment to practice somersaults. I must have looked like a rabbit in the headlights but once I got going the talk flowed, the video worked and all went well. The room was packed, with people even standing at the back to hear the talks from myself, Angela Douglas, Sia Polihronis and Shashikant Kulkarni about how we have implemented the Genetix GSL-120 slide loader into the workflow of our laboratories. Once it was over, we headed back to the main hall for the opening ceremony which was followed by a talk by Felix Mitelman about cancer chromosomes through the ages.

Speaking of the baby, Stockholm is a good place to be pregnant given the price of alcohol. One (very sober) delegate reported finding a bar charging £25 a drink! Genetix kindly took the speakers and our colleagues out for dinner on Saturday night to a Swedish restaurant. The food was amazing – chilled spicy tomato soup, fresh fish with vegetables and the most amazing strawberry and fennel dessert, not to mention the local spirit, Aquavit, which smelt great and I'm told tastes pretty good too!

Sunday saw us back at the conference centre bright and early to hear Victoria Leggett from Oxford University present the results of a study into the outcomes for children with sex chromosome abnormalities. Lisa Shaffer outlined the changes that had been made to the recently published ISCN 2009 and after a lunch break with a couple more packed satellite symposia from Abbott and Perkin Elmer, Maj Hulten, Renee Martin and Lucia Migliore gave us an insight into their recent work on the origin of aneuploidies.

That evening we headed to a reception at Stockholm City Hall where the annual Nobel prize awards are held. This is a stunning building, situated by the river. We got to walk down the staircase that the prize winners descend to receive their honours. It's designed with a window on the opposite wall to focus on so that prize winners can look straight ahead whilst descending the stairs wearing ball dresses and heels. I couldn't do it in trainers so it's just as well I'm never going to get a Nobel prize!

On Monday, the luggage saga continued with some UK delegates still not being reunited with their bags. Darwin was brought into the 21st century with engaging talks from Malcolm Ferguson-Smith, Pat Heslop-Harrison, Mariano Rocchi and Michael Lynch. In the afternoon, Dieter Kotzot gave us a review of UPD syndromes and the mechanisms by which they arise followed by a useful

session on quality control and accreditation. John Wolstenholme discussed the interpretation of prenatal mosaicism and Thomas Liehr presented information from his database about low-grade mosaic marker chromosomes and their clinical interpretation.

By Tuesday the elusive luggage had finally arrived just in time to accompany its owners on their journey home! There was a stampede to get a space in the Agilent satellite symposium and after the keynote lecture by Thomas Cremer, poster prizes were awarded and the conference was officially closed and we said goodbye to Stockholm and headed home. Hopefully everyone's luggage made it back too.

The only things that marred an otherwise great conference were the new trend for flash photography, accompanied by twinkly camera noises during talks, along with mobile phones ringing and being answered. Hopefully this will not catch on at UK conferences as it caused a considerable amount of distraction to both speakers and audience members.

Rising Down syndrome diagnoses and terminations and falling numbers of invasive diagnostic tests: who will count them next year?

Professor Joan Morris, Director of the NDSCR, Queen Mary University of London

There was considerable media interest in research published by the National Down Syndrome Cytogenetic Register (NDSCR) in the British Medical Journal in October about the increases in the number of Down syndrome diagnoses and terminations in England and Wales (see BMJ 2009;339:b3794 doi:10.1136/bmj.b3794). All the data reported was directly from your cytogenetic laboratories. Thank you for supplying the data!

Last year we asked laboratories if they would supply us with information on all amniocentesis and chorionic villus samples (CVS) processed (not just those that were found to have a trisomy) for 2008 and any earlier years if possible. So far 18 out of 21 laboratories have kindly provided their data and we are currently coding it to make the codes consistent across labs and hope to finish analysing it in the near future. Figure 1 is a preliminary analysis of data from one cytogenetic laboratory and it shows the number of amniocentesis and CVS procedures that were performed per Down syndrome case detected from 2000 to 2008.

There has been an enormous reduction of around 65% (from 40 to 15 for amniocentesis, and from 15 to 5 for CVS). This is solid evidence of improvements in screening resulting in fewer, unnecessary invasive diagnostic tests. This information should be of vital interest to those monitoring the screening programme for Down syndrome.

The recent media attention highlighted that the register is the only reliable source of information on Down syndrome in England and Wales, as government statistics under-report both terminations and births. Despite this fact, the register is currently only funded until March 2010. We are actively searching for new funding, and would appreciate any advice on potential funding sources.

If the register is no longer funded – who will be counting Down syndrome next year?

Thank you once again for providing the NDSCR with your data.

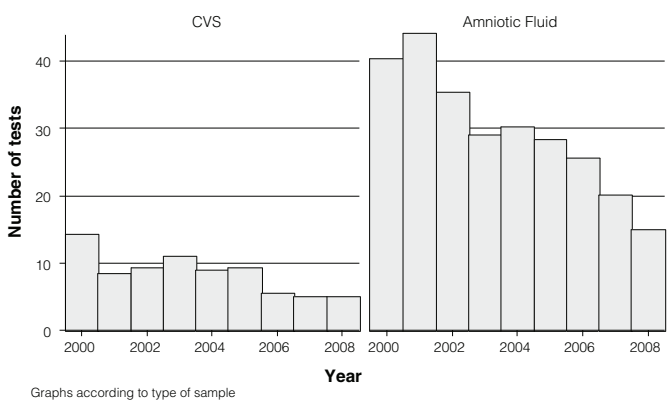

Figure 1

Trends in Down syndrome live births and antenatal diagnoses in England and Wales from 1989 to 2008: analysis of data from the National Down Syndrome Cytogenetic Register

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Between 1989 and 2008 two changes occurred that influenced the numbers of diagnosed Down syndrome pregnancies. First was the considerable increase in maternal age, which is a major risk factor for Down syndrome. Second was the increase in antenatal diagnoses of Down syndrome, which included non-viable fetuses that would not have survived to term and therefore would not have been diagnosed previously.

This study describes the trends in the numbers of Down syndrome live births and antenatal diagnoses in England and Wales from 1989 to 2008. It used data from the National Down Syndrome Cytogenetic Register, which holds details of 26488 antenatal and postnatal diagnoses of Down syndrome made by all cytogenetic laboratories in England and Wales since 1989.

Figure 1 shows that despite the population numbers of births in 1989/90 and 2007/8 being similar, antenatal and postnatal diagnoses of Down syndrome increased by 71% (1075 in 1989/90 to 1843 in 2007/8). However, the numbers of live births with Down syndrome fell by 1% (752 to 743; 1.10 to 1.08 per 1000 births) because of antenatal screening and subsequent terminations. In the absence of such screening, numbers of live births with Down syndrome would have increased by 48% (from 959 to 1422), since couples are starting families at an older age. Among mothers aged 37 years and older, a consistent 70% of affected pregnancies were diagnosed antenatally. In younger mothers, the proportions of pregnancies diagnosed antenatally increased from 3% to 43% owing to improvements in the availability and sensitivity of screening tests.

Therefore since 1989, expansion of and improvements in antenatal screening have offset increases in Down syndrome resulting from rising maternal age. The proportion of antenatal diagnoses has increased in younger women, whereas the proportion in older women has stayed relatively constant. This trend suggests that even with future improvements in screening, a large number of births with Down syndrome are still likely, and that monitoring of the numbers of babies born with Down syndrome is essential to ensure adequate provision for their needs.

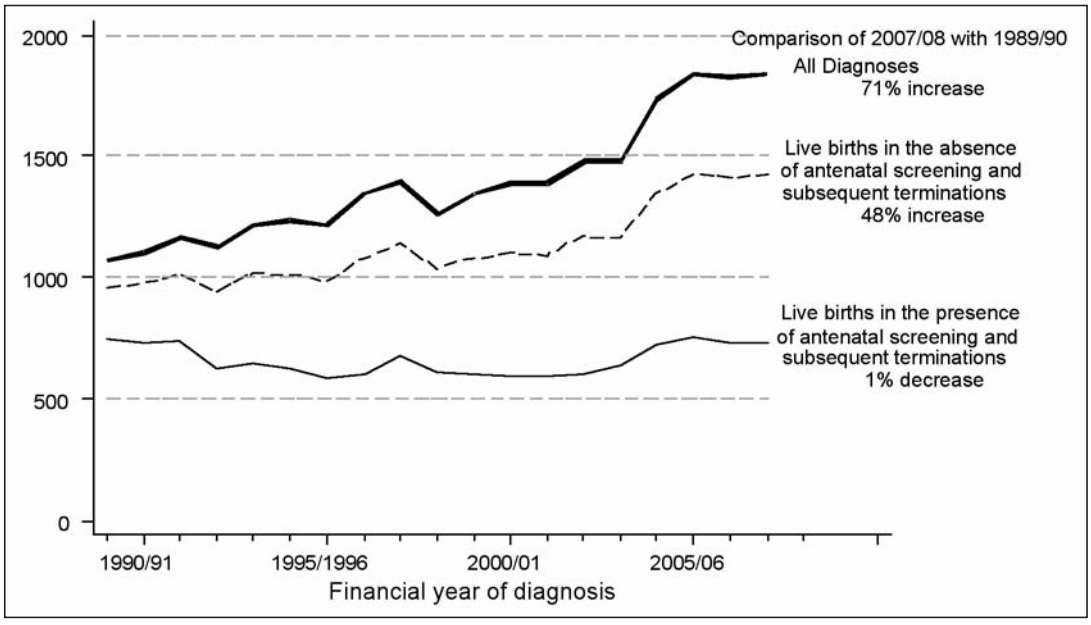


Figure 1 : Downs syndrome diagnoses and live births according to year of diagnosis and the presence or absence of antenatal screening and subsequent terminations

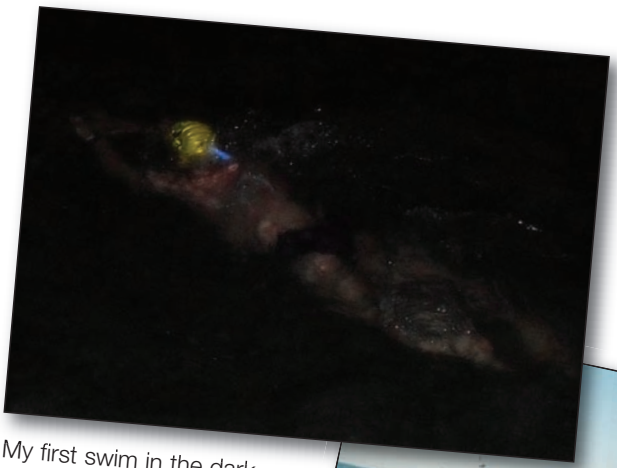
Day trip to France

Mark Sales, Dundee

My name is Mark Sales and I am a Clinical Scientist in the Cytogenetics lab at Ninewells Hospital in Dundee. I was fortunate enough this year to be able to swim the English Channel as part of a relay team. I would like to say thank you to all the people who sponsored me for the attempt, I have so far raised £1000 for St. Luke's Hospice in Cheshire (http://www.justgiving.com/Phibbies-channel-swim-Mark-Sales if anyone would still like to donate).

I have been open water swimming for 2 years now; I first started on a charity swim across the river Tay organised by a local radio station. Unfortunately poor conditions meant we ended up swimming round and round the harbour instead! I joined a local open water swimming club, Ye Amphibious Ancients Bathing Association the following year and finally made it over the Tay. I have been swimming in the balmy (!!) waters of the Tay ever since; crossing the river a number of times, tackling longer swims (4 & 8 miles tidally assisted) and crossing the River Forth. This year I was asked if I wanted to be part of a relay team to swim across the English Channel to celebrate the club's 125th anniversary.

I, along with 5 other club members, spent much of the year training, and finally on 23rd September we headed down to Dover. Unfortunately, we found out the boat was broken and we would need to wait at least a day for it to be fixed. The go ahead was given on Friday 25th and we headed off to meet the boat just after midnight. The team set off on an hour-long trip to Shakespeare Beach where we would start the swim. At 2.20am Lynsey, our lead off swimmer, swam from the boat to the beach (in the dark!) and then headed out to sea.; each swimmer would do a 1 hour shift. I set off for my swim at 5.20am when it was still pitch black, although I had a lovely blue glow-stick tied to my head so that the boat crew could see me! This was a bit freaky at first but then felt quite nice with the boat beside me. Then I realised that all the pretty lights I could see around us were the ships in the busiest shipping lanes in the world! All you could see were their running lights and sometimes their shadow as they passed another ship. It was getting light at 6.20am when I handed over to the next swimmer. Fortunately we had great weather conditions, as this was when I realised I suffered from seasickness and threw up over the side! My next stint swimming in the sun with the sea very calm was a great feeling, even though we could now see all the huge ships around us as we headed through the second shipping lane. Some of the ships were huge, and it often looked as if they were heading straight for us before they passed behind. At the end of the swim, we all swam in with the last swimmer and made landfall just beside Cap Gris Nez. It was a fantastic feeling to have eventually made it to France after 15 hours of swimming. However fate had a twist in store for us. We headed back to the boat only to find that it had got stuck on a sandbank and the tide was going out! We did try and give it a push but it was stuck fast. The only thing to do was wait until the tide came back in, which it did at 3am Sunday morning. Eventually the boat floated enough that the engines could push us over the sandbank and we headed off, arriving back in Dover extremely tired, but very happy.



My first swim in the dark

The Team (l-r) Me, Claire, Lynsey, Ricky, Mary-Rose, Beth

Rob Morgan 1957-2008

Jeff Williams, Leeds

By the time this edition of the BHSG newsletter has been published it will have been just over a year since Rob Morgan passed away on 27 October 2008 after a long battle against cancer that was initially diagnosed back in 1997.

Rob came to the Leeds Cytogenetics laboratory having graduated with a BSc degree from Nottingham University which he had followed up with an MSc in Radiation Biology. Rob was initially employed on the old, now defunct, scale as "probationary scientist", a title that will be familiar to all us old timers and rapidly climbed the Cytogenetic career structure to become Principal Cytogeneticist and head of the postnatal section. He developed numerous interests along the way including a self taught interest in Information Technology. Rob was a good listener, extremely popular with his colleagues particularly those junior members of staff who needed assurance and motivation and always provided sensible and appropriate advice. Rob made a significant contribution to professional life and was an active committee member of the Federation of Clinical Scientists from 1990-2008. In this role he was actively involved in the introduction of Agenda for Change which would have been more problematic than it turned out to be if it was not for his involvement. Rob was also assistant secretary of the ACC for a number of years.

Rob was a keen sportsman, starting off playing squash when he first came to Leeds. Rob was a big guy weighing about seventeen stones and had enough trouble moving quickly in a squash court but had even more difficulty stopping suddenly in a solid box and soon came to the conclusion that squash was not for him. He then began playing rugby and could have played to quite a high standard if it were not for his illness. Rob's main sporting interest in the past few years was golf, developing a style and swing all of his own which had never been described in any coaching literature and was certainly not to be copied. Last summer saw the first inaugural golf competition for the "Rob Morgan Cup" attended by his family, friends and colleagues and this will now become an annual event.

We soon came to realize what Rob had contributed to the Leeds Cytogenetics laboratory when it came to organising cover for those activities which he had developed and assumed responsibility for. What he did and what we had taken for granted had to be absorbed by a number of senior staff.

Rob was an extremely pleasant man and did not let his illness affect his outlook on life remaining cheerful and positive to the end. Many people who worked with Rob were not aware of his condition until the later stages.

Rob is survived by his wife Elaine and two daughters Alison and Katherine.

Rob will be remembered and missed by his friends and colleagues in Leeds and also by those who he worked with nationally.

ACC Spring Conference 2010 – Keble College, Oxford. 12-13 April 2010

The Oxford Cytogenetics Laboratory look forward to welcoming you to the city of dreaming spires for the 2010 ACC Spring Conference.

We aim to provide a comprehensive scientific programme, with notable guest speakers, poster presentations and a bioinformatics training session, all of which will be located within the beautiful and impressive grounds of Keble College.

Monday evening's entertainment will commence with a reception held in the Oxford University Museum of Natural History. This will be followed by the Conference Banquet, held in Keble's grand Dining Hall, opened in 1878.

The ACC conference will be followed by a joint ACC/CMGS meeting located at St Catherine's college, a short walk away from Keble.

Contact details and more information including scientific programme, accommodation, travel and registration details can be found on the conference website:

www.springmeeting.cytogenetics.org.uk

Genetic Technologist Study Day 1 October 2009 Birmingham Women's Hospital

Frankie Shaw, Cambridge

A National Genetic Technologist (GT) Study Day on the 1st of October 2009, was hosted by Birmingham Women's Hospital. Sarah Warburton, National Trainer for the Clinical Molecular Genetic Society, organised this event for the benefit of Molecular Genetic and Cytogenetic Technologists. This was the first joint study day of Genetic Technologists from both disciplines.

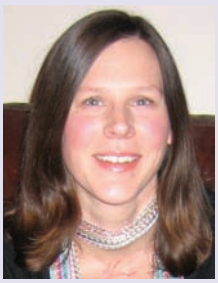
This event was attended by 92 GTs from all over the UK. The agenda included updates on Modernising Scientific Careers and presentations on working practices in the Liverpool laboratory. The latter included a comparison of the advantages and disadvantages of disease-based versus technique-based working practices in the Liverpool and Cambridge Molecular Genetics laboratories and how integration of the two genetic disciplines might be achieved in the future. GT training schemes are currently being piloted in several UK labs and the presentation by Sumera Ghani of her experience at Great Ormond Street Hospital, London highlighted the benefits of gaining skills in both disciplines.

Michelle Fenlon presented information on the Association of Genetic Technologists Committee and their role on the Voluntary Registration Council (VRC). She emphasised the importance of encouraging GTs to become members of their respective professional bodies. The Health Professions Council (HPC) requires an aspirant group to have at least 25% of the work force as members of their professional bodies before an application for registration will be accepted. Currently, the VRC has 7 aspirant groups with a total of 157 registrants, of which 109 (69.4%) are Genetic Technologists. Clearly the message is getting through; however with over 700 GT's in the country who will need registration at some point, the VRC requires more people to apply to the ACC and CMGS for membership. Membership provides discounted rates for conferences and access to travel grants. State registration has the advantage of maintaining the Agenda for Change band levels for laboratory staff and the automatic transfer of registrants to the HPC register when the application has been accepted.

The afternoon session consisted of Molecular Genetic presentations on DNA extraction techniques using paraffin-embedded tissue, microsatellite instability, pyrosequencing, a QF-PCR case study and implementation of semi-automated sequencing. Two Cytogenetic presentations outlined the use of FISH probes on products of conception and placental samples to identify aneuploidy in pregnancy loss and reduce the failure rate in tissue culture. The presentations also highlighted the use of FISH to identify patients who may be at increased risk of progressive cervical disease if a gain of chromosome 3q is identified in their cervical smear sample. Presentations were voluntary and are available on the CMGS website member's area.

Many thanks to Sarah Warburton and Birmingham Women's Hospital for a very enjoyable day and we look forward to further Genetic Technologist study days in the future.

ACC News Editors



Deadline for contributions for next issue is 30 November 2009

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Editorial

Vicki Wiles, Principal GC, East Anglian Medical Genetics Unit, Cambridge

Welcome to the AGNC section of BSHG News. Ann Kershaw, who has edited this section for the last three years, has stood down from the role as she has now joined the Editorial Board of BSHG News. I would like to thank her on your behalf for taking on the work of Editor when she already had more than enough to do in her joint managerial and clinical role as Consultant Genetic Counsellor and Genetic Counsellor (GC) Manager.

I have taken over as Editor from this edition. The Registration Training Panel has provided a very interesting overview of the Genetic Counsellor Training Scheme to date and plans for the future. You will see that there is an update from the GC Registration Board (GCRB) on changes to the Registration process and news from the AGNC committee. There is also a report from the CGG's (Cancer Genetics Group) conference held in Glasgow and finally an interesting article from Nicola Coates, GC, who won an AGNC travel award to attend the Huntington Disease World Congress meeting in Vancouver.

As Editor I plan to explain acronyms wherever possible, because I find I forget what they stand for all too easily. And, following the recent discussion on Yahoo group email , I shall be approaching each Clinical Genetics centre in turn, asking them to submit a summary of their team, services offered and a photograph, so that we can keep in touch with what is happening and where. I plan to use the reverse alphabet method to select the next centre, using the name of the city or region where the centre is based.

Lastly, articles are very welcome from any members. The format and style is outlined in BSHG News Issue 41, June 2009, pages 10 and 11.

Genetic Counsellor Training Post Scheme: an update Training Post Scheme Panel

Background to the scheme

The commitment, set out in the Genetics White Paper, to increase the genetic counsellor workforce by at least 50 posts through support for existing and new training opportunities is well on its way to being met through the Genetic Counsellor Training Post (GCTP) scheme. This scheme is profession-led and monitored, and funded by the Department of Health.

A total of 17 Centres were approved for genetic counsellor training and 43 trainees were appointed in the first two phases of the scheme. Approved Centres needed to provide access to a comprehensive learning environment suitable for genetic counsellor training, including a multidisciplinary approach to patient care, a named registered/eligible for registration genetic counsellor to act as a training supervisor/mentor and clinical and counselling supervision.

Appointment to the training posts was very competitive, with up to 70 applications received after advertisement for individual posts. This has meant that the GCTP scheme has been able to attract individuals with a high degree of commitment and enthusiasm.

Professional and educational backgrounds of trainees

One of the primary aims of the scheme, to ensure a diversity of backgrounds amongst the genetic counsellor workforce, has been achieved.

- Around one in three trainees (37%, n=16) had a professional background in the health or social services, mainly in nursing. Four of these trainees had an MSc in Genetic Counselling in addition to a professional background.
- Half the trainees (51%, n=22) had a scientific background and an MSc in Genetic Counselling.
- The remaining five trainees had neither a health professional background nor a Genetic Counselling MSc, but were graduates who used their training post to obtain an "entry-level" MSc (permissible only in the first phase of the scheme).

Outcome data: the current situation

- The majority of the 43 trainees (88%, n=38) now hold a substantive genetic counselling post in a Regional Genetics Centre
- About two-thirds of past-trainees (63%, n=24) obtained a post in the Centre in which they trained, with the remainder moving to practice in a different Centre.
- Three trainees are still in their training posts.
- Only two trainees left their posts for employment other than genetic counselling, one of whom completed her training as a genetic counsellor.

Professional registration

The GCTP scheme was designed to enable trainees to develop the competencies and prepare the portfolios required for UK genetic counsellor registration. Of the 38 former trainees in post, 14 are now Registered Genetic Counsellors, with another 12 having submitted their portfolios to the Genetic Counsellor Registration Board in the current annual round of applications for Registration. The remaining past-trainees plan to submit their portfolios next year or as soon as they are eligible to register.

A different way of doing the same thing

Kathy Barnes, Chair, Genetic Counsellor Registration Board (GCRB)

The next phase of the scheme

The GCTP Panel, the AGNC Committee and the Genetic Counsellor Registration Board remain committed to the continuation of structured training posts and approval of training centres. Recently, the GCTP Panel have been successful in obtaining DH funding for a third phase of the scheme which will enable the White Paper commitment of 50 new genetic counsellors to be realised.

In this third phase, the DH will part-fund ten new training posts by providing 50% of the trainee's salary and on-costs, as well as providing generous funding for an educational allowance and a training centre stipend. The GCTP Panel will professionally monitor the new phase of the Scheme.

Once DH funding was confirmed, Centres were invited to apply for re-validation as a genetic counsellor training centre. All re-validated centres were able to apply for training post funding after confirming that their host Trust would meet 50% of the salary and employment costs of a trainee. Mentors in the scheme must be Registered Genetic Counsellors.

This process in currently underway as we write, but it is hoped that all new trainees will be in post before the end of the current financial year.

This will be the final phase of the DH-supported scheme. However, we hope that this part-funded scheme will encourage many departments to embed a training post within their budgets for the future.

The GCTP Panel will also be pleased to monitor non-DH funded training posts in a similar manner to the DH posts. If any Centre has such a post, we would be pleased to hear from them.

Genetic Counsellor Training Post Scheme Panel

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Registration of genetic counsellors has been running for seven years now and overall the process has developed in an efficient and satisfactory way.

However over these years we have listened and reacted to comments made by board members, assessors, mentors and those going through registration. One constant theme had been the consistency of marking the portfolios. Comments and concerns have been voiced by all – but mostly by those actually doing the assessing. Some of these concerns have been around knowing what constitutes Master's level, how to discover plagiarism or feeling uncomfortable about being too harsh, or too lenient. The assessment process is, in reality, down to personal interpretation.

We have had fantastic input from Diana Scotcher and Annette Robinson in the training of the assessors and it is thanks to the work they have done that the assessment process has worked at all. We hope that they are going to stay with us, but the work they do might change.

Before I continue, there is a background story to tell. Please join me on a trip to Blankenberge, Holland, at the Huntington's Disease Conference in 2006. I was sitting in the sun enjoying a coffee and chatting with a relatively new Board member, Pat Finnemore. Pat and I were having a very detailed discussion about the assessment process and Pat told me, with great enthusiasm, about a system she took part in, which involved a group of experts meeting together at a specific time to look at and assess the work of those wishing to be considered for the qualification. We agreed that this method

AGNC Committee News

Cath King, Bath

of gathering together a well chosen and trusted team to read and discuss the work, and appoint a mark, seemed a fair and foolproof way of doing things.

Many months later the Board looked at this system again and decided that, although we could see the potential, it was too risky – almost too brave – to attempt change. And it was consigned to being a good idea that would require a real determination to introduce. But since then, and in response to comments by all those taking part in portfolio assessment (whether being assessed, doing the assessing or looking on from a Board perspective), we have increasingly felt that things could be done in this new way if we would only dare to make the change.

Move forward to sunny Cambridge in June of this year when a small group of GCRB members met at Anna Middleton's house to really thrash out the idea. We had Skype input from Clara Gaff in Australia, where a very similar method is used, with excellent results. This was extremely helpful and gave us the reassurance that the system works and even more material with which develop the idea. By the end of the day, we had a plan to build upon.

Here is a brief outline. The portfolio and the evidence contained therein *will not change*. What will change is who sees the evidence. Essentially, the mentor will endorse and sign off such data as competencies, case-log, continuing professional development and reflective records of counselling. The three case studies and the essay will be submitted to the Board administrator and *anonymised*. This work will then be sent to those who are going to constitute the marking panel. This work will be read and marked and brought to a final meeting when all the work will be reappraised and given a pass or deferred. This written work will then be linked with the owner's portfolio and only at that point will the identity of the candidate be revealed.

Initially, the marking panel will constitute Board members and others who have experience in this area. Because the work is anonymised, there should be no conflict of interest. There will be a moderator present. We hope to have a rolling programme of people who will be asked to join the panel. The role of the Mentor will be increased in responsibility with the new duty of 'signing off' certain sections of the portfolio.

We are going to introduce this new method of assessment in 2011. By then we will have fine-tuned the timetables and guidelines and hopefully picked up on potential pitfalls. I am depending on your support and patience and I do hope that you will appreciate that, after much thought and discussion, we will see increased efficiency and trust in the genetic counsellor registration process.

As many of you will be aware, the AGNC committee has been working on guidelines for genetic counsellor job plans. An increasing number of centres have been asked to formalise their practice in this way, and the committee therefore felt that it would be helpful to produce templates that could be used as guidance, but that could also be adapted to suit local needs. These job plan templates are now complete, and will be on the website in the near future, for general use.

Next year will see some major changes in the committee, as both Gilly Bromilow and Jen Wiggins will be standing down next year, from their roles as Chairperson and Vice Chair respectively. This means that there will be two vacancies on the committee, so please give some thought to those you feel could make a valuable contribution, and encourage them to stand for election. Although we were hoping to introduce an electronic voting system for this election, it will require a change to the constitution, and we plan to address this issue at the AGM, held at the Spring Meeting on 29 April 2010 at St. George's Hospital. In the meantime, this current round of elections will still be paper based, and ballot papers will be distributed in the New Year.

We have also received news from the Genetic Counsellor Statutory Regulation Steering Group (GCSRSG) that they will be presenting our case for statutory regulation by the Health Professions Council (HPC) to the HPC on 10 December 2009. This is earlier than anticipated, due to the high standard of the application paperwork produced by this group, who have been working extremely hard to drive this forward on behalf of the membership.

The Department of Health have also agreed to part-fund a further ten trainee posts. All

current training centres have been required to re-apply for validation, and those accepted will shortly be able to bid for these posts.

The AGNC Spring Meeting 2010 will be held on Thursday, 29 April, at St Georges Hospital, London. The first call for abstracts can be found on the AGNC website, and the electronic abstract submission page will be available from 1 December 2009. If you have work to present, but funding to attend meetings is an issue, you could always consider applying for an AGNC Award; details are available from the AGNC website.

We are hoping that members will not only be keen to present their work, but also volunteer for other activities related to such meetings, such as abstract scoring, or chairing a session. Opportunities also arise for members to represent the AGNC on various national working groups and committees, and we would like these opportunities to be open for all members. We are therefore intending to expand the career opportunities page on the AGNC website to include volunteer opportunities as well as job opportunities, so bear this in mind if you would like to become more involved with such activities.

Finally, we would like to thank Janice Stein, editor of the Journal of Genetic Counselling for allowing AGNC members free access to the Journal for a further year. The Journal can be accessed through our website, and the password can be obtained from your AGNC regional representative. Please do not contact our overloaded website co-ordinator for this information. If you don't know who your regional representative is, contact details can be found on the AGNC website.

2009 World Congress meeting on Huntington Disease

Nicola Coates, Guy's, London

The 2009 world congress meeting on Huntington disease (HD) was held in the Westin Bayshore hotel which sits against the beautiful backdrop of the mountains and harbour of English Bay in Vancouver.

Each day began with a plenary session, followed by science and care sessions running simultaneously. The first day began with stories from four people living at risk of developing HD. This included a 13 year old girl who gave a very moving account of the discovery of HD in her family and how she had coped with living at risk of HD.

The science session focused on imaging, clinical and cognitive biomarkers which could be used to indicate the presence and progression of HD as well as the effectiveness of a given treatment. Stefan Kloppel talked about imaging (MRI) studies which have indicated a complex pattern of structural and functional changes in HD affecting a number of cortical and subcortical regions of the brain. These studies have shown that the largest change in the size in the striatum is seen prior to onset of HD. Ralf Reilmann explained that current systems of measuring clinical biomarkers are categorical, insensitive, subjective and unreliable, particularly in pre-symptomatic HD mutation carriers. His group has developed more objective and sensitive measures which use force transducers to measure subtle variations between subjects and controls. These biomarkers are awaiting validation, but preliminary data suggests that both types of biomarkers can detect changes 10-20 years before onset of HD.

The afternoon care session looked at approaches to symptomatic therapy for HD. It was noted that there was a lack of research into effective treatments, with most current treatment being based on expert opinion rather than research results. A useful talk of practical significance was the assessment and intervention for gait and balance in HD. Use of the four-wheeled walker with front swivel castors, produced the most consistent and safe gait pattern in HD patients when compared with five other mobility aids. The video game *Dance Revolution* was helpful in improving cognition as well as gait and balance and was very popular with subjects.

Day two included a series of lectures on inflammatory and metabolic changes in HD. Marcy MacDonald focused on the huntingtin protein which appears to play a role in regulating aerobic and anaerobic respiration. Her group has also specifically looked at the role of the polyglutamine region (which if expanded causes HD) by looking at a series of huntingtin knock-out mice and huntingtin CAG knock-in mice and cell lines. Their results suggest that the polyglutamine region further modulates energy metabolism and that increasing its length decreases energy metabolism.

Patrick Weydt summarized the research into the transcriptional master regulator PPAR-gamma co-activatorα (PGC-1α) in one of a number of talks on possible modifiers in HD. PGC-1α has been shown to be repressed by mutant huntingtin and may play a role in HD pathogenesis. His data suggested that certain common single nucleotide polymorphisms (SNPs) in the PGC-1α gene are associated with a significant delay in age of onset of HD.

Cancer Genetics Group meeting in Glasgow

Catherine Watt, Glasgow

On the final day, Sarah Noonberg and Karl Kieburtz presented details about the HORIZON study which is a new worldwide phase III study looking at the effect of Dimebon (latrepirdine) in HD patients. This drug has been shown to enhance cell survival, which speakers suggest may be through stabilizing mitochondria. Dimebon has previously been shown to benefit cognition, behaviour, activities of daily living and overall function in a randomized double-blind study of mild to moderate Alzheimer disease patients. There have also been promising results in early trials with HD patients.

In the late breaking HD research session, Holly Kordasiewicz presented some optimistic work on antisense oligonucleotides (ASOs). Using ASOs her group have been able to selectively diminish mutant huntingtin protein in brain and peripheral tissues in mice. Their study showed that injecting ASOs into the brains of R6/2 mice (an HD mouse model) at 8 weeks prevented 75% of the loss in brain mass from 8 to 12 weeks compared to R6/2 controls. They are now studying mice at an earlier stage to see if brain cell loss can be completely prevented.

My thanks go to the Guy's Multidisciplinary HD clinic, the Clinical Genetics Department, Guy's Hospital and the AGNC for funding me to attend this conference. Abstracts have been published in Clinical Genetics; Volume 76, Supplement 1, September 2009.

The United Kingdom Cancer Genetics Group Spring Conference was held in Glasgow in May 2009 and was organised by Ms. Nicola Bradshaw Macmillan Genetic Counsellor. Nicola was elected to the UK CGG in 2007 and at one of her first meetings, in the style of Mario Puzo's Corleone family the CGG committee made Nicola an offer she couldn't refuse. Nicola accepted the challenge of organising the 2009 Spring Conference and with the help of colleagues, Ruth Cole and the administration team the two day meeting was a great success. The posters, scientific programme and invited speakers were interesting, varied and promoted lively discussion amongst the delegates. The conference party was dinner followed by very energetic ceilidh dancing and I am pleased to report that there were no fatalities. It is also important to note that Nicola managed to arrange two consecutive dry, sunny days in Glasgow – amazing.

Congratulations Nicola!

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AGNC Travel Award Report

Dr Anna Middleton, Consultant Research Genetic Counsellor, Cardiff

I attended a cancer genetics conference on 23-24 November 2009 in London; this was made possible by travel awards from the AGNC, Cancer Genetics Group (CGG) and support from the Department of Health. This meeting brought together delegates and professional members from several different groups: Cancer Genetics Group, British Association of Surgical Oncology, Association of Cancer Surgery and Association of Breast Surgery.

The conference included a wide variety of sessions, most of which were pitched perfectly towards health professionals working clinically with cancer patients, with a particular focus on breast cancer. The following areas were covered: molecular genetics of cancer (eg, 'polymorphisms in epigenetic regulation genes, breast cancer susceptibility and prognosis'), clinical cancer genetics (eg, 'role of the geneticist in breast cancer management and risk assessment tools'), oncology (eg, 'primary endocrine therapy for early operable primary breast cancer'), pathology ('micrometases and isolated tumour cells – are they important in prognosis or are we over staging?'), screening ('identification of men with a genetic predisposition to prostate cancer: targeted screening of BRCA1/2 mutation carriers'), surgery (eg, 'efficacy of risk reducing mastectomy – a worldwide review').

The Cancer Genetics Group sessions were particularly interesting; there was one specific presentation that I was very keen to attend on the use of SNP analysis for breast cancer and the clinical utility of this. There are now 18 SNPs within low and moderate genes involved with breast cancer. Paul Pharoah from Cambridge University discussed the clinical application of SNP testing – suggesting that in the future SNP analysis will be added to our current toolkit for breast cancer risk assessment and that it should be possible to create individualised breast screening programmes for women based on their personal risks rather than broad risks from family history alone. There was debate at the coffee break about how this is perceived generally within the profession, with concern that it is too soon to implement SNP analysis into NHS clinical assessment. Discussions ensued about what would happen if patients had SNP analysis done via a private company and were told that they had a 'raised risk' on the basis of this, but had no significant family history that would meet current criteria to access NHS screening. Personally, I feel that we should be prepared for the eventuality that patients will come to us having had a SNP analysis done privately, there are companies offering this now (eg, Breast Health UK). It is therefore helpful to have thought through in advance what we will be able to offer such patients in terms of information and interpretation of SNP results.

There was a very interesting presentation on the NHS Breast Screening Programme (NHSBSP)– this programme will now incorporate all the screening needs of genetics patients. The recall of genetics patients will happen nationally for each individual genetics patient and will remove the current postcode lottery for mammography screening. MRI scanning will also be available through NHSBSP. This is also a massive shift from what is currently available. I also learnt that use of the term 'prophylactic mastectomy' is outdated and that 'risk reducing mastectomy' is preferred.

This conference was excellent and will form a valuable contribution to my CPD hours required for renewal of genetic counsellor registration. I am particularly grateful to the funding bodies for enabling me to attend this meeting.

AGNC News Editor

Deadline for contributions for next issue is 30 April 2010

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Editorial - Moving into the main stream of medicine…well done Sir John!

Sue Huson, Manchester

The interesting thing about being editor is I find myself thinking…'must do an editorial about that'- usually this is to moan about something e.g.when I am faced with yet another course I must attend as part of Trust policy. Fortunately for you all, this editorial remains unwritten! This one is all about celebrating the success of our specialty in gaining recognition as part of main stream medicine. Many people deserve credit for this…but the person I will name is John Burn. It was fantastic to see his name in the New Years Honours list… he does such a great job of sharing his enthusiasm for our discipline with people of all walks of life.

My only regret is that John's old 'sparring' partner, the late Robin Winter, is not around to help John celebrate. I can just imagine the wit and repartee between them about John's knighthood. It seems appropriate therefore to follow this article with a piece remembering Robin. Our colleagues at GOS have had a sculpture commissioned in his memory – Elisabeth Rosser shares her memories of Robin and a picture of the sculpture.

Whilst on the subject of achievement, we end with Shane McKee telling us about his sponsored bike ride for the 'English Hospital' in Nazareth.

In between we have a series of feedback articles from CGS council and the SAC. Their contributions reflect a lot of hard work for which we must all thank them. They contain vital information about plans for revalidation, clinical governance and the recent update of the genetic training curriculum.

On the clinical front we have two important articles. One describes the new nationally commissioned (NCG) Ehrlos Danlos Syndrome service and the other the PONTI trial looking at prevention of neural tube defects with inositol.

I have now been editor for nearly three years. We have recently heard from NCG that our proposed national NF2 service is to be funded from April 1st. On a personal level this means I have finally become a 'one disease' Doctor (although I do all types of NF!)…as such I am not sure I am the best person to be your editor. So volunteers please to susan.huson@cmft.nhs.uk !

Sue Huson

Professor Robin Winter remembered…

Elisabeth Rosser, Great Ormond Street

Most people reading this will be aware of Professor Robin Winter's outstanding contributions to the field of Clinical Genetics, but those who have joined the speciality in recent years will not have seen Robin in action. I will recap his achievements for them. Robin was one of the first trainees appointed to the Senior Registrar posts in the developing speciality of Clinical Genetics in1978 together with Dian Donnai and Ian Young. He was a consultant at the Kennedy Galton Centre initially, then moved to Great Ormond Street.

Robin was one of the great dysmorphologists, and clinical teachers. A brilliant thinker and researcher, he, together with Michael Baraitser, developed the Winter-Baraitser Dysmorphology and Baraitser-Winter Neurogenetics Databases. Despite his formidable academic achievements he was a clinician at heart and was appreciated, respected and loved by both his patients and colleagues. Sadly, Robin died in January 2004, after a short illness.

We have finally bought a sculpture for the GOS department to remember him by – not that an object is really needed. It is a chromosome created out of copper: with copper wire over a layer of beaten copper. The accompanying picture doesn't really do the sculpture justice – it is a three dimensional object and no one who has seen it so far has been able to resist touching it. It is in the department of Clinical Genetics at GOS and anyone who would like to come and see (and touch) it is welcome.

The chromosome was made by Sandra Reeves and will be featured on her website in the near future.

Letter from the President

Frances Flinter, Guy's and St Thomas', London

www.wiredandfired.co.uk. Sandra has no scientific background and researched both chromosome structure and Robin's work while making the chromosome. She described it as a privilege to be asked to make something in his memory. Those of us who knew Robin, would also describe that as a privilege.

There are quite a few initiatives to report on so I will summarise them briefly below. As always, please get in touch if there is anything you would like to talk about or propose for discussion to the CGS council.

House of Lords report into genomic medicine

Many colleagues have been involved in responding to this report through various routes. There were a number of positive recommendations, and of course the continuing high profile of genetics is welcome; but some concerns have been expressed about the incomplete understanding of the current roles of clinical geneticists and the extent to which we are already involved in counselling patients with multifactorial conditions. A response from the Department of Health is imminent.

Recruitment into Clinical Genetics

Surprisingly, we seem to have fewer applicants for training in Clinical Genetics than previously and it is not clear why. Opportunities to promote the specialty are being identified e.g. at careers' fairs. In addition, a number of regional centres are moving away from the national recruitment scheme for specialist registrars and doing their own local recruitment, which allows them to advertise and interview for posts at a time that is convenient for them, attracting candidates who want to work in the part of the country. It is important to have the support of the local Deanery in order to do this, but centres that have made this transition are finding it works better.

Clinical Governance

I am delighted that Sarah Smithson is raising the profile of the work on clinical governance in our specialty. The CGS council is keen that we all learn from studies done in particular centres and wants to ensure that useful resources are readily available to everyone.

GMC revised Guidance on Confidentiality

As you are probably already aware, revised guidance was issued recently and one of the most significant changes relates to situations when it is considered appropriate to disclose genetic information to relatives without the consent of the proband.

www.gmc-uk.org/confidentiality

Preimplantation Genetic Diagnosis (PGD)

Problems persist in obtaining funding from PCTs for PGD. Currently providers have to ask PCTs for funding on a case by case basis and decisions are sometimes inconsistent and inequitable. The Human Genetics Commission has performed a survey of PCTs (which has shown that many do not have guidance to help guide their decision making) and also of providers, who have identified significant delays in obtaining decisions and clear evidence of inequitable decisions in different areas. I hope that the Genetics Commissioning Advisory Group will address this problem in the near future.

ACCEA

Congratulations to the many clinical geneticists who were successful in obtaining Clinical Excellence Awards in 2009. The Society is allowed to nominate 6 colleagues for bronze awards, two for silver and two for gold. In the last round all the nominations that we made were

awarded and many colleagues who had not applied for CGS support, but who applied through their local Trusts and/or the College of Physicians also did well. The College invited the society to provide a citation for anyone whom it was considering and so we were able to support a number of colleagues by this route as well.

British Library archiving

The British Library and the Welcome Trust are working together on a project to archive the websites of specialist societies; CGS has signed a licence agreement allowing this to happen. In future years it may prove interesting to look back at the sorts of things we have on our website now. Adam Shaw works hard to keep the website informative and up to date, so please look at it and let us know if there is anything that you would like to add or amend.

http://www.clingensoc.org/

The Welcome Trust has also offered to archive other records that we hold which could be of interest to researchers in future. If you have any relating to CGS work that you feel might be relevant please could you let me know?

HGC consultation Framework of Principles

There is some consensus that a form of regulation might help to help protect the general public from possible harm following the purchase of genetic tests either over the counter or via a non-genetically qualified intermediary. The HGC has drawn up a draft Framework of Common Principles describing what good practice could look like in any country, which could be used to derive specific local Codes of Practice in individual jurisdictions. I have asked Alan Fryer to lead on the official CGS response as I was involved in drawing up the consultation document, but I hope that individual clinicians might also consider responding too. Please have a look:

http://www.hgc.gov.uk/Client/Content.asp?ContentId=816

HGC/NSC working party on preconception genetic screening

The National Screening Committee has received the comprehensive review on Tay Sachs screening that was prepared by the PHGF and has now asked the HGC for advice on preconceptual vs antenatal screening. A working party will be convened shortly to consider the issues.

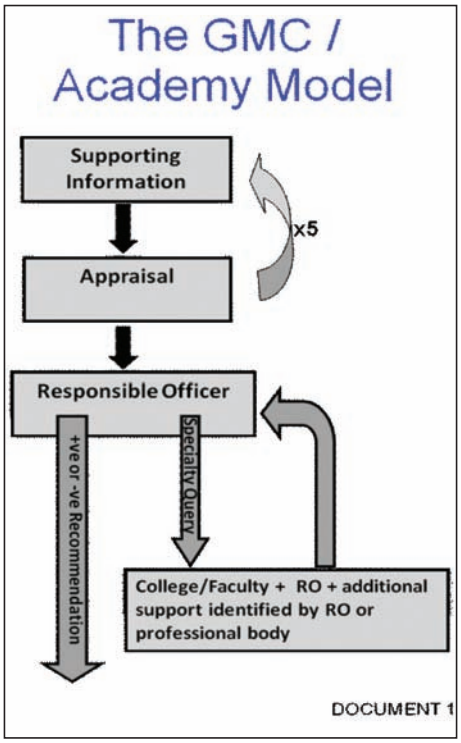
Finally, it is appropriate to acknowledge that in the current financial climate we must all be prepared to think imaginatively about ways of continuing to deliver efficient and effective clinical genetics services within the constraints of shrinking budgets. One way in which we can all help each other is by sharing good ideas so please let me know if there are any that I can help to promote, and good luck. I look forward to hearing from you.

Revalidation update

Alan Fryer, Liverpool

The overall process

A simplified view of the process that is expected to be approved is given below. In addition the RCP would like doctors with concerns to be able to directly approach the College/Responsible Officer.



The RCP has input as follows:

1: defining standards, developing and validating specialty tools and providing specialty guidance for appraisers – we as a specialist society will probably need to give advice with regard to what guidance should be given to appraisers and appraisees in our specialty, above and beyond the generic standards (see below).

2: providing specialty support and advice where specialist queries are raised as they arise and wherever appropriate.

3: quality assurance of the outputs of the appraisal and revalidation process through an audit of recommendations. It is not the RCP's responsibility for quality assuring the processes that go on within Trusts but if an external QA is performed, the College would like to be informed of outcomes. The RCP will however be involved in the training, support and monitoring of appraisers and may want to audit a sample of all positive recommendations (the London College are in favour of this but not the others at present), all negative recommendations, all whose revalidation process causes concern to the R.O. or the doctor and all where an "agreed statement of concern" is to be issued. This could be a huge task with major resource implications – not something that can be squeezed into SPAs!

There is no specific role here for the specialist societies.

The RCP's input at a local level will be through a network of regional advisors and Regional Specialty Advisers (detailed arrangements may differ between RCPL and the two Scottish Colleges)

- Regional Advisors and Specialty Advisers will be trained on the Colleges' policies and procedures with regard to revalidation – in particular the Physician Medicine Framework based on the GMC's revised framework for appraisal and assessment, and on the checklist of supporting information.
- Regional Advisors will act as a conduit for ROs to give them access to an up-to-date national network of Specialty Advisors
- Initial contact by ROs, physician appraisers, and individual doctors will be through the Regional Adviser (Service) or other named local lead revalidation adviser who will involve Specialty Advisers where required.
- National Networks of specialty and sub-specialty advisors will be available to advise (co-ordinated by regional advisors) ROs, Regional Advisors, physician appraisers, and individual doctors on the standards for, and interpretation of, supporting information related to particular physician specialties and sub-specialties.

The appraisals

The RCP recommends that Physicians should be appraised by another physician and wherever possible by a physician in the same sub-specialty.

It has been suggested that at least one appraisal in a five year cycle should be with someone from another specialty, and the implications of this are being explored.

As stated above, we as a specialist society may need to give advice with regard to what guidance should be given to appraisers and appraisees in our specialty. There will probably be an RCP template developed so that these guidelines will be in a similar style across specialties. The RCP are producing a document "Revalidation for Physicians" which details a number of items on a "core checklist" and a number of items on an "optional checklist" which could inform the process. On the core list are

- Case-based discussion and/or case-note review
- Anonymised patient referrals and responses
- Logbooks, where appropriate
- Observed clinical practice where appropriate and agreed
- Portfolio record of cases discussed or reviewed with peers or other colleagues

We may need to provide guidance as to how much evidence would be expected in these categories for a clinical geneticist. It is very subjective and difficult. When published we are requested to put this document "Revalidation for Physicians" on our website.

In addition, each subspecialty may wish to ensure the professional competence of its physicians by requesting specific items of supporting information that reflect the work of the specialty or subspecialty. However it is important that these map to the core headings of the Physician Checklist, and thus serve to support the Attributes of the GMC Framework, without creating an additional bureaucratic burden for those working in specific subspecialties. Some specialties have sent in suggestions for this – notably those with procedural skills or national audits - the RCP are going to send a template round so that these specialty-specific items fit the checklist.

Some specialist associations will also provide complementary guidance about tailoring the collection of supporting information - for example, the Physician Medicine Framework will request that an audit is brought to appraisal and the specialist association guidance may recommend a particular sub-specialist audit.

What about knowledge assessment?

I have written to J Med Genet to ask what their view would be of linking questions to review articles - this is being discussed by the editor and BMJ Publishing and I am awaiting a reply.

Clinical Genetics Curriculum review 2009

Mary Porteus, SAC Chair, Edinburgh

Every two years the Postgraduate Medical Education and Training Board (PMETB) conducts a review of the curriculae for higher specialty training. As Chair (acting until someone works out an appropriate selection process) the 2009 review was my responsibility. I had a hard act to follow; the previous two SAC chairs, Helen Kingston then Sally Davies had each more than risen to the challenge. Fortunately the result of all their hard work was a robust 2007 curriculum to morph into the required format for 2009.

The "challenges" (as we management types describe them) for 2009 were the inclusion of leadership competences, health inequalities and the mapping of assessment methods. A workgroup of volunteers and a few specially selected representatives was formed- at the risk of sounding smarmy, I have never worked with such a collaborative and functional group – everyone did what they said they would. Sarah Smithson tackled the health inequalities. Paul Brennan, always up for a challenge, waded into the leadership competencies declaring that he had "never seen so much utter waffle." Chirag Patel, clearly a book editor in a previous life, did a fantastic job grooming the competencies of the 2007 curriculum and we were fortunate to be supported in our task by Hannah Watts, the project manager, who managed and circulated each new version of the curriculum, checking and reformatting.

After one London and one Edinburgh meeting and a lot of e-mail communication the curriculum was complete and was submitted to PMETB prior to the formal review meeting which was scheduled for 18th November. Sarah and I volunteered to meet the review panel.

The RCP are interested to know what knowledge assessments are in place (if any) and would specialist societies want the RCP to try and look at links to the RCP CPD system.

Specialty-specific MSFs- We were asked to provide 5 questions to be piloted. We submitted the following:-

1. Written communication: uses appropriate terminology in letters to patients and colleagues

2. Ethical issues: demonstrates appropriate understanding and practice of ethical aspects of genetic history taking and investigation, including consent and confidentiality in families.

3. Performs appropriate investigations and makes appropriate referrals to other specialists

4. Regularly discusses clinical problems with colleagues.

5. Follows appropriate guidelines in relation to predictive testing

The RCP are collaborating with a commercial company "360 Clinical" to develop an electronic system to validate the questions and see whether they have additive value. The process will be piloted through Trusts that utilise this company. Individuals will be able to log in, select the specialty and then complete the generic questions and then the specialty-specific questions and these specialty specific questions will be sent to specified groups – i.e. just doctors, just doctors and nurses, therapists etc, all respondents.

Audit-RCP want to know if specialist societies would be interested in an audit tool – perhaps 5 questions focused on what an individual learnt from the audit – not the actual data itself.

Collecting the supporting information

RCPs will support their members by providing an E-system to hold specialty specific supporting information.

This e-portfolio will be College-based and not DoH – nobody trusts any DoH IT system!! It will be simple and is being developed with buy-in from most colleges and faculties. They are agreeing a simplistic specification and there will be physician-specific , surgeon-specific versions etc. but with a common summary.

It will have 2 tiers – summary information – THIS IS SENT TO A CENTRAL APPRAISAL SYSTEM (and may be publically accessible) and a second tier with detailed information which can be shown if asked (e.g audit data). The summary may be simply audits done and what changes in practice have resulted – not the actual audit data. They hope to develop the system in the next 12-18 months (??).

We may be asked what sort of information we want captured in this e-portfolio.

Feedback from the Clinical Governance Committee

Sarah Smithson, Bristol

PMETB is housed in an unimposing multi-occupancy building in Lambeth with inadequate lifts. Sarah and I opted to take the stairs to the seventh floor and arrived somewhat breathless in a stuffy room littered with the detritus of a high fat lunch. On the way up the stairs, the charming panel administrator assured us that there was no cause for concern; indeed the panel was keen to point out the strengths of the curriculae they had reviewed. I was unconvinced and, asked how we would ensure that those coming in from paediatric or core medical training would have the same competences, launched into a passionate speech about core values in genetics and the need for a range of experience prior to entry. The panel looked more and more confused until Winnie Wade, education director for the College, tactfully stepped in with the answer " they use the same portfolio". We spent some time discussing how we were planning to deliver the specialty certificate exam – again lots of hand waving on my part. The panel chair then admitted that they were finding it hard to come up with essential questions as our curriculum was so well written and succinct. I suspect it may have been more to do with the lunch.

Thanks to the working group:

Judith Goodship, Alistair Kent, Ruth McGowan, Alex Magee, Chirag Patel, Sarah Smithson, Hannah Watts

The CGS Clinical Governance Committee has undergone some changes this year. We would like to thank John Dean and other former committee members for their work over the past four years. Current membership includes 3 council members (Sarah Smithson, Emma Hobson and Anneke Lucassen), an additional consultant member (Helen Murphy), a SpR representative (Rachel Cole), 2 genetic counsellors (Carol Giblin and Margaret James) and a member of GIG (Christopher Friend). After discussion with Council earlier this year the committee decided to approach Clinical Governance in three main themes: patient safety, quality and clinical effectiveness. All the UK Clinical Genetics centres have governance leads (in some cases this is the lead clinician) who have indicated their agreement with this approach and willingness to share information. Our work in progress is described below.

Patient safety

We have recently contacted the 24 Governance Leads to ask about their experience of clinical incidents. The point of this is to identify for our specialty where risk may occur and to encourage discussion about what we can do to anticipate or avoid risk. We will be consulting the National Patient Safety Agency and the NHS Litigation Authority to understand the origin of perceived or established harm to Clinical Genetics patients. Anneke and colleagues are currently updating the 1994 guidelines on genetic testing of children and consent and confidentiality for BSHG. These issues clearly relate to safety and quality and will be very helpful in our clinical practice.

Quality

There is increasing emphasis on providing high quality services for NHS patients and evidence to demonstrate them: this is now part of good medical practice. The National Quality Board has established aims and work programmes to ensure high quality in the NHS. Furthermore, according to the CQuIN framework, a proportion of future provider income will be conditional on showing quality and innovation. The Royal College of Physicians ran an interesting workshop in September on the role that Specialist Societies may play in addressing these agenda. In clinical genetics it is perhaps less obvious what parameters may be chosen to demonstrate high quality than in other specialities. Many other physicians have had to address very stringent quality measures such as infection rates for MRSA and C. Difficile. There will be the opportunity for specialist societies such as CGS to comment on specific topics identified by the National Quality Board and the onus is on us to engage with them. A key theme is the paramount importance of involvement of patients in service development. Patient surveys are a good way to start and the Governance committee has suggested that we have one endorsed by CGS for optional use and also invite people to share their existing surveys. We intend to develop an area of the website for this purpose.

Clinical effectiveness

The committee has also approached genetic centres in the UK about sharing guidelines or care pathways currently in use. These could also be made available on the CGS website, the original authors and centres to be fully acknowledged. Several colleagues have already indicate their willingness to help and have sent guidelines to us.

We would like to thank everyone for their help and co-operation in developing Governance strategies for Clinical Genetics and please do contact us if you have any specific ideas or comments.

sarahh.smithson@UHBristol.nhs.uk

A nationally commissioned service for Ehlers-Danlos Syndrome

Mike Pope, Kennedy Galton Centre and Glenda Sobey, Sheffield

From 1 April, 2009, the North West London Hospital NHS Trust, together with the Sheffield Children's Hospital NHS Trust have received joint funding from the National Commissioning Group (NCG) to provide both a quaternary clinical assessment and diagnostic laboratory service for patients with complex forms of Ehlers-Danlos Syndrome (EDS). The successful bid was led by Dr Ann Dalton and Dr Angela Brady in collaboration with Dr Glenda Sobey and Professor Michael Pope. The service operates on two sites: Clinical Genetics, Sheffield Children's Hospital and North West Thames Regional Genetics Service, Kennedy Galton Centre, Northwick Park Hospital.

Dr Glenda Sobey is the Clinical Lead at Sheffield, whilst Professor Pope has been appointed until 2012 to initiate the Clinical Service at Northwick Park and also to train a proleptic Consultant Clinical Geneticist to take over the London service after that date. Both teams are supported by secretarial/administrative staff and genetic counsellors, and strong collaborative links are already in place between the two sections with regular interactive joint clinics, interdepartmental data sharing and joint clinical diagnostic protocols. The diagnostic laboratory service is split between the two sites, with molecular genetic testing centralised in Sheffield, whilst both laboratories will address collagen protein diagnostic screening, fibroblast culture and light and electron microscopy. Currently COL3A1 sequencing is available for vascular EDS and related disorders, as is COL1A1 and COL1A2 analysis for EDS VIIA & VIIB families. COL5A1 and COL5A2 analysis for appropriate classical EDS families and PLOD1 analysis for EDS VIA families are planned.

We would like to take the opportunity in this article to clarify which types of patients are eligible for assessment by the new service.

Why EDS?

The service closely conforms to NCG policy which covers clinical services of between 400 and 1000 consultations per annum. Initially there is a consultation target of 400 families per annum shared between the two sites. Consultations are specifically limited to EDS families referred from consultant specialists, such as clinical geneticists, dermatologists, rheumatologists, paediatricians, orthopaedic surgeons, neurologists, neurosurgeons and gastroenterologists, in which the diagnosis is suspected but unproven. These include complex diagnostic overlaps with other inherited defects of connective tissue, in which EDS is likely.

Which patients are eligible?

The clinics and laboratory service are funded to receive referrals from England and Scotland. Referrals from elsewhere, such as Wales and Northern Ireland are also eligible but they will be charged the relevant clinic/laboratory tariff.

The referral criteria are as follows:

- Diagnostic criteria according to Villefranche Classification not met
- Diagnostic testing does not confirm diagnosis suspected
- Diagnostic criteria of more than one type of EDS identified
- Significant additional findings aside from diagnostic criteria
- Complex clinical, therapeutic or diagnostic management problems

Referrals are also accepted where the patient or clinician requests a second opinion after initial secondary and tertiary consultation.

Current service arrangements?

Patients referred are seen for clinical assessment in one of the EDS specialist clinics, dictated by geographical location or patient preference. Appropriate specimens will be taken at the appointment. Patients will be reviewed in joint MDT meetings using video conferencing. For more complex problems combined clinics are held at both Sheffield and London.

The Sheffield DNA laboratory already provides UKGTN COL3A1 testing for vascular EDS. Therefore where the clinical diagnosis is clear patients need not be seen in the specialist service. However testing of ambiguous or suspected vascular EDS families can be accommodated by the new service, to select those individuals in whom testing is justifiable. Similar considerations apply to other EDS families, such as those with undiagnosed EDS I/II, VIA or VII, in which future gene analysis of the COL5A1,5A2,COL1A1,1A2 or PLOD1 genes are relevant.

How to make a referral?

Please do not hesitate to contact us informally if you wish to enquire about whether a patient would fit the criteria for this service.

Prevention Of Neural Tube Defects by Inositol

The PONTI trial – now recruiting

Can inositol increase prevention of neural tube defects in conjunction with folic acid?

The PONTI Trial team, London : Victoria Shepherd, Andrew Copp, Lyn Chitty, Nicholas Greene,Therese Hesketh

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Neural tube defects occur in 0.5 to 2 per 1000 pregnancies when the embryonic neural tube fails to close in the third and fourth weeks of gestation. Periconceptional administration of folic acid has been shown to be highly effective at preventing NTDs with randomised clinical trials in the UK and Hungary demonstrating a 70% reduction in recurrence1 as well as a preventive effect on first occurrence of NTDs.2 However, evidence from clinical trials, fortification programmes and case studies indicates that a subset of NTDs, perhaps 30-50%, are not preventable by folic acid.

There is evidence to suggest that a proportion of the NTDs that are folate-resistant may be preventable by another substance called inositol. In mice, inositol deficiency leads to NTDs and supplementation with inositol in pregnant mice can reduce the frequency of NTDs.4,5 Furthermore, there is a significantly lower concentration of inositol in the blood of mothers carrying NTD fetuses than in normal pregnancies.3 In case studies, three women who had suffered two previous NTD-affected pregnancies (despite folic acid supplementation in at least one pregnancy), took inositol supplements (0.5 g per day) as well as folic acid in the first trimester of subsequent pregnancies. A total of five pregnancies were uneventful and unaffected by NTDs (two women had two pregnancies)6,7.

Inositol is a naturally occurring nutrient and is widespread in many foods. Inositol therapy appears to be completely safe. Detailed pathological analysis of inositol-treated mice revealed no major fetal defects and no increase in fetal loss. Moreover, the women who took inositol in the 5 documented pregnancies did not report any adverse effects. Trials in adults with psychiatric disorders, in autistic children, and in infants with respiratory distress syndrome have all demonstrated benefits with no side effects. Relatively high inositol doses have been used: up to 18 g per day in adults and 200 mg/kg in children.7-10. It seems unlikely therefore that exogenous inositol therapy will pose a risk to the mother and/or embryo/fetus.

We are now carrying out a pilot study to determine the feasibility of performing a definitive randomised, double blind clinical trial comparing folic acid alone with folic acid plus inositol for the prevention of neural tube defects. This initial pilot project is taking place in the UK and we need to recruit 100 women to each arm of the trial. If the pilot is successful we plan to continue to a full-scale trial, with inclusion of collaborating centres in other countries in order to recruit the estimated 900 cases per arm to achieve a statistically significant result.

This study has been approved by our ethics committee and the MHRA, and the inositol and placebo tablets have been manufactured and fully tested, especially for this trial. The study is now in progress and we are seeking to recruit women who have a history one or more NTD-affected pregnancies and who are planning a further pregnancy. Women who are taking anti-epileptic medicines are excluded, as are women where the neural tube defect was due to aneuploidy or suspected to be part of a genetic syndrome. The study consists of a simple two-arm trial protocol. All subjects receive identical folic acid supplementation at the 'high dose' level of 5 mg, recommended for use in pregnancies at risk of NTD. In one

arm of the trial women will additionally receive inositol at a dose level of 1 g daily, consistent with previous clinical trials. Placebo will be given instead of inositol to members of the control group.

Women may enter the trial by different routes: referred by their GP or obstetrician or through self-referral. We are also raising awareness through relevant patient support groups. Folic acid and inositol/placebo are prescribed by the UCL Institute of Child Health, according to a double blind protocol. These are mailed to the women directly, with clear instructions for their use. Supplementation begins prior to conception and continues until the 12th week of pregnancy. We are monitoring compliance by measuring the level of inositol in the maternal urine. Pregnancy outcome will be determined by second trimester ultrasound scanning, plus follow up of pregnancies at term. Contact with the women is by phone, email and letter and we will not be asking them to travel to us in London (documentation and urine samples are simply mailed to us in provided packages). Unfortunately, for the pilot trial, we do not have funding to enable translation of the patient information leaflets or interpreters and so we will have to confine recruitment to women with a good command of English.

We will happy to answer any queries that you may have. Our trial coordinator, Victoria Shepherd, is based at the UCL Institute of Child Health and can be contacted by email at pontistudy@ich.ucl.ac.uk or by phone on 0207 905 2822 or 07772 258243 Alternatively, Nicholas Greene can be contacted by phone on 0207 905 2217. Local ethics approval will not be required for your participation - all we are asking is that you put us in contact with likely trial subjects. We will do the rest. Information packs will shortly be sent to all genetics units containing more information, as well as leaflets to give to appropriate families. We really do need your help with this trial and will be most grateful for your co-operation.

For more information email us: pontistudy@ich.ucl.ac.uk

See also: www.pontistudy.ich.ucl.ac.uk

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Crossing the Jordan - Amman to Nazareth

Shane McKee, Belfast

Many of us who have trained in medicine have vivid memories of our fourth-year electives, some good and some bad, and often we look back on them as formative periods in our personal and professional lives. I have often wondered how things had changed at the Nazareth EMMS Hospital in Israel in the years that have passed since I was there in 1993. Referred to locally as the “English Hospital”, for many years it has actually been run by a Scottish Christian charity. It is now staffed and attended mainly by local people, Jews, Muslims, Christians, Druze – all faiths and none.

Nazareth is the largest Arab town in Israel, and the melting pot of cultures is reflected in the hospital itself. The old days of the expatriate doctors are now gone, but what has emerged is something of a model for co-operation, mutual respect and community development in the Lower Galilee in northern Israel, where inter-community tensions can still bubble up from time to time. Each year the UK supporters of the hospital organise a cycle challenge to raise money for its work, so I decided to get on my bike.

The School of Nursing in Nazareth has one of the most impressive programmes in the entire Middle East. It has had the highest pass rate for the national exams in Israel for the last three years, and is making great strides. Young men and women from all the communities and religious groupings of the Lower Galilee are being trained to the highest standards, and bringing those skills and values back to their local areas. The funds from this year's bike ride are to help provide bursaries for students from disadvantaged backgrounds in the Galilee to study in Nazareth, as well as to help with infrastructure projects at the hospital itself.

With the fading embers of my thirties guttering in the grate, I decided to have my mid-life crisis early, and get fit at the same time. There were 20 of us in the group, including our excellent guide and the tour doctor (not me, thankfully) who was tasked with looking after some of the more senior members of the group. Our plan was to cycle from Amman in Jordan down to the Dead Sea, and along the Jordan Valley, eventually ending up in Nazareth. It was to be a circuitous and scenic (i.e. hilly) route of about 250 miles, affording us an opportunity to see Israel and Jordan from a very different perspective to the usual tourist exposure, as well as providing a tough but achievable challenge.

We started on 2 November, cycling down to the Dead Sea from Madaba, to the south-west of Amman. Day two was a real challenge, facing some serious hills on the climb up to Jerash. Day three took us to the Israeli border, where the mosquitos enjoyed a hearty supper before we cycled in the dark to the kibbutz of Neve Eitan, and we got our own hearty supper. On day four we cycled to the eastern shore of Lake Tiberias before catching a boat for a sunset crossing to Ginosar. The final day took us up some more hills to Nazareth, the goal of our journey.

On arrival at the hospital, after some more tricky hills, we were greeted by the local scouts and their brass band — a warm welcome which really helped to dull the aches in our legs and other bits that I probably shouldn't mention. The hospital has developed a great deal since my last visit, and it was a real privilege to meet some old friends, as well as some

of the neonates in the Baby Unit — a new generation of Nazarenes. We also met many of the nursing students who will benefit from the funds raised. The future of the Nazareth Hospital looks bright.

I am really grateful to all the people who have sponsored me, especially my many friends in Clinical Genetics in the UK and beyond. Health care is one of the great uniting factors in the world, even when the petty concerns of religion and politics introduce divisions and misunderstanding. Positive change comes from establishing human relationships and common goals that transcend superficial categories of "Arab" or "Jew" or "Muslim" or "Christian" or "Atheist". The region still has its troubles to contend with, but in many ways we're all in this together.

My sponsorship page is at http://justgiving.com/shanemckee and a blog of my training and travels (with some random metaphysical whimsies) is at http://answersingenes.blogspot.com

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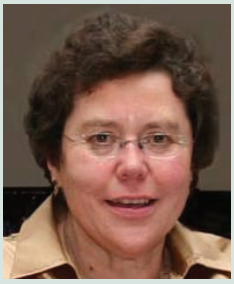
CGS News Editor



Deadline for contributions for next issue is 30 April 2010

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Editorial

As we go to press, one is settling into ones new office accommodation, with views of the foothills of the Pennines (that is, on a good day – today one can see all of 400 yards!). The laboratory accommodation is very generous, as the estate agents say, and offers uninterrupted views over Manchester. The newly-equipped lab finally ditched its old DNA extractor: protocol dictates that one cannot name the manufacturer – suffice to say, it was the size of a bus and broke down twice as often! The new one (different make!) is the size of a small mini-van and has only lost one batch of samples so far; so that's progress, I suppose.

On the subject of working tools, what do you do when your philanthropic founders and benefactors give you (another) $400 mill? You spend some of it on new toys, of course! The Broad Institute has just shelled out a few bucks (amount undisclosed!) on 30 (gulp!) new Illumina 'Genome Analyzer' systems. Why, one might enquire? Because they like them, apparently! (See "News from The Web" below).

Thanks once again to the contributors to this issue: we have an excellent crop of articles as per usual. First up is Ian Frayling's report back from the International Society for Gastrointestinal Hereditary Tumours (InSiGHT) meeting in Düsseldorf in June 2009. Ian's very readable copy is intelligible even to non-cancer types like me and makes very interesting reading. One of the many high quality presentations concerned the modification of Colorectal Cancer (CRC) risk by testing a number of SNPs, thereby altering the likelihood of the requirement for surgery. The new term "surgicogenetics" springs to mind – remember you heard it here first, folks! Ian also refers to an article by Sharon Plon – who is trying to quantify risks associated with UVs – which is worth looking at if only to see a mention of the most contrived acronym in genetics: the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA). How far do we have to stretch the English language, just to render something memorable?

In a related article, Joanne Campbell reports from the Third International Symposium on Hereditary Breast and Ovarian Cancer, held in Montreal in October 2009. Once again, very informative and readable, and, once again, reference to Sharon Plon, but this time we're talking about VUS's. Can we at least agree on what they're called: UVs or VUS's? Or shall we let HGVS decide (they'll come up with c.p.SHUVUPs, or something like that!)?

Next, congratulations to Natalie Bibb, formerly of KGC, Northwick Park, who took home the CMGS Best Poster prize from the Warwick meeting (see below) – yet more cancer stuff, readers!

Please also pay attention to the advert from UK NEQAS who are recruiting to the Steering Committee. It's not only very rewarding, but also allows you to try to change all those things you complain about every time the QA samples appear!

Finally, a bumper crop of stuff from the Web. First off, congratulations (I think) to Francis Collins on his Papal Appointment. Researching this gave me an opportunity to browse the Vatican Website – now there's an eye-opener! I dare say Dan Brown has been its most frequent visitor these past years.

Secondly, a gene for bad driving! Well, a poly in BDNF, but even so guys, we've at last got an excuse! No truth in the rumour it's on the Y chromosome!

Thirdly, congratulations to our long-time collaborator from ICI Diagnostics (as it was then), Steve Little, who borrowed a few quid of venture capital and turned it into a genotyping business worth $130million. The company, DxS, was sold to Qiagen for such a sum – a tad better than he ever managed on his visits to the dog track!

Next, on a more serious note, I'm delighted that someone is taking an interest in recurrent mutations (albeit in the cancer field – again!). This seems to be an area that has never hit the big time but, like CNVs, seems to be growing in significance in the diagnostic arena.

And finally(!), something to warm the cockles over the winter months: a US District Court has thrown out a motion by Myriad *(inter alia)* to dismiss a lawsuit brought against them by the American Civil Liberties Union (a collective of numerous interested parties including patients and researchers) on the grounds that such small fry shouldn't be allowed to sue Big Pharma (I paraphrase, naturally!). ACLU were suing on the basis that Myriad's BRCA patents were not only illegal, but also unconstitutional. By the time we go to print, we should have heard more of this case, which is clearly set to run and run!

A Happy New Year to All Our Readers! One hopes you all enjoyed your mid-winter festival of whatever denomination.

Martin Schwarz

InSiGHT 3rd Biennial Meeting: June 2009

Ian Frayling, Instiute of Medical Genetics, University Hospital of Wales

The International Society for Gastrointestinal Hereditary Tumours held its 3rd biennial meeting in Düsseldorf (http://www.insight-group.org/meetings/dusseldorf2009/).

At a pre-meeting, collaboration was discussed between InSiGHT, the Human Variome Project (Dick Cotton) and the NIH Colon Cancer Family Registry (USA; Steve Gallinger), in order to address the issue of interpretation of unclassified variants in Lynch Syndrome (LS). Sean Tavtigian reported back from the IARC meeting in February, making the point that family history (e.g. Barnetson R et al NEJM 2006; 354:2751-63 and https://hnpccpredict.hgu.mrc.ac.uk) and tumour testing data could be fed into a model to generate probabilities of pathogenicity. Five classes of probability of pathogenicity were proposed: p <0.001; 0.001-0.05; 0.05-0.95; 0.95-0.00; >0.99 .(as in Plon SE et al (2008) Hum Mutation 29,1282-91. Hence, it was now necessary for such phenotypic data to be gathered in the InSiGHT LSDB, and work to be done on real-world variation in estimates. This will then be taken forward to a meeting of the HGVS to be held next year. Subsequently, DMuDB and InSiGHT are working together on how UK data may be added to the InSiGHT LSDB, which is already the third largest LSDB.

There was also a meeting of those interested in PMS2 families. Phenocopies, i.e. sporadic colorectal cancers (CRC) with microsatellite instability (MSI), loss of MLH1 and PMS2, and BRAF V600E are often seen, and are probably an artifact of ascertainment bias consequent upon clinical referral criteria, i.e. the necessity to have a family history. Parents ascertained by children who are homo- or compound heterozygous for PMS2 mutations have little if any family history.

A session on GWAS in CRC nicely demonstrated that 10 SNPs confer 6% of general familial risk of CRC (i.e. not LS), while 100 SNPs would give 80% and 172 SNPs would give ~100%, but there are many issues, such as population heterogeneity, rare private variants, and gene x gene x environment effects. Richard Houlston summarized the intriguing data on known modifiers of LS: CYCD1 G242A increases penetrance of MSH2, but not MLH1; MTHFR T677 and C1298 have little effect alone, but together they reduce the average age of onset by 15 y. The age of onset is also less in those with an IGF1 dinucleotide repeat of <18, and the shorter the repeat the younger the age.

Juul Wijnen presented work on new SNP modifiers. He had looked at the top 14 SNPs associated with population risk of CRC, and asked the question if they were modifiers of LS, using the huge set of families available in Leiden, and indeed, some appear to be. The C allele of rs16982766 (8q23.3) confers a three-fold increased risk of CRC in males, but not females, while rs3802842 at 11q23.1 confers a three-fold risk of CRC in females, but not males. SNP rs4355419 (4q13.1) doubles CRC risk in males. Any three risk alleles (out of the 14) confers even more risk. Assuming other studies confirm these findings, this degree of risk modification warrants more individually tailored surveillance and/or prophylactic surgery, and it will probably not be too long before testing for modifying SNPs is introduced into clinical practice.

Interesting data was presented from Germany on the immunology of LS patients. Frameshift peptides (FSP), as would be expected to be expressed in tumours with microsatellite instability, were predicted in silica from the human genome sequence, and then synthesized in vitro, to make an antigen array that would detect antibodies in vivo. This showed that FSP antibodies are detectable even in LS patients who have never been diagnosed with tumours. Perhaps this is evidence of subclinical tumours, and such autoimmunisation may confer an increasing degree of protection with increasing age? Also, it has been known for some time that HLA Class I expression is lost in MSI tumours, due to B2M or HLA A2 coding microsatellite mutations, thus enabling such tumours to evade immune surveillance. However, it is now evident that such tumours also lose Class 2 expression, as a result of CIITA 1962_1963insC, RFX5 56delC, RFXANK, or RFXAP mutations: clearly they are under great selective pressure to evade the immune system.

Megan Hitchins presented a family with a transmissible MLH1 epimutation, unlike earlier MLH1 epimutations which were in individuals and not transmitted. Evidently, this will now need to be considered in families with e.g. tumour evidence of a MLH1 mutation, but nil found on sequencing & MLPA.

Three talks on EPCAM/TACSTD1 illustrated that different deletions of this locus upstream of MSH2 are all capable of causing LS. However, analysis of five families with a common Dutch mutation (EPCAM c.859-1462_*1999del) reveals that curiously, while they are prone to

CRC and small bowel cancers like classic LS, only one family was classifiable as Amsterdam positive, and no cases of endometrial cancer were observed. Testing for these mutations may warrant a lower/different threshold than for testing MSH2/MLH1.

John Burn presented the CAPP2 study data indicating that treatment of LS patients with aspirin, for a defined period, confers a longstanding protection against colorectal and endometrial cancers. This was discussed by Riccardo Fodde, who presented data that this is evidence of an effect at the level of so-called cancer stem cells, and he asked for collaboration in gathering fresh LS tumour tissues to explore this.

Some preliminary data on CNVs was presented by Ramprasath Venkatachalam, who had found that in 32 cases of young onset, but microsatellite stable, CRC he observed 5 novel CNVs. He had investigated dup PTPRJ/DEP-1 on 11p11.2 in particular, because it contains a candidate human tumour suppressor gene/ mouse susceptibility locus. On testing 1500 cases and controls of familial CRC, he found 2 dups and 4 dels of this region in the cases (more than expected by chance), and all of various sizes. Why both dels and dups are associated with the same phenotype is a mystery, but this shows (if it were needed) that CNVs have a bearing on cancer, as with probably every other human phenotype.

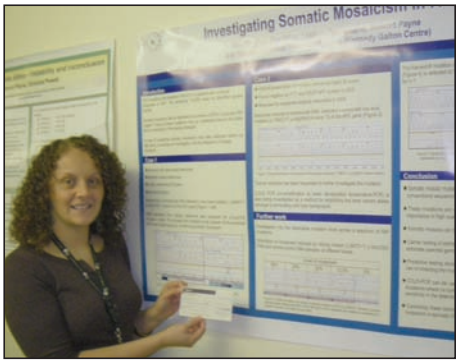
In a session on mismatch repair (MMR) immunocytochemistry (ICC), Susan Parry from New Zealand showed that it was useful in investigating young onset CRC, while Louise Klarskov (Denmark) had studied inter-observer variability in ICC reporting, and found that both tyros and so-called experts were equally variable. I then presented the initial findings of the UK NEQAS ICC MMR, which show that ~50% of participating laboratories score <12, which is borderline acceptable, and that certain staining protocols are much better than others.

Elke Holinski-Feder showed that MUTYH mutations had now been observed in a wide variety of phenotypes: FAP, AFAP, and Atypical FAP. While Julian Sampson presented the results of a large collaborative study showing that the CRC standardized incidence ratio in MUTYH carriers is 2.12 (1.3-3.3). Even in this well controlled study, this may be due to biases such as ascertainment via family history clinics, but nonetheless, it is the risk observed in the population which attends clinics.

So, much to consider and some exciting findings in respect of modifier SNPs and CNVs. Now it just needs incorporating in some Best Practice guidelines!

Congratulations Natalie!

Stewart Payne



Natalie Bibb from the Kennedy-Galton Centre (KGC) at Northwick Park Hospital was awarded the CMGS prize for "Best Poster by a Pre-Registration Scientist" at this year's BSHG conference in Warwick. The poster, entitled "Investigating Somatic Mosaicism in FAP" describes the finding of an APC nonsense mutation during mutation screening of lymphocyte DNA from a patient with colorectal polyposis. The low peak height of the variant in Mutation Surveyor generated sequence trace suggested somatic mosaicism. This was confirmed by sequencing DNA extracted from archival tumour tissue where the peak heights of the mutant and wild type nucleotides were roughly equal indicating true heterozygosity in colonic mucosa. Natalie then went on to conduct mixing experiments in order to explore the limits of visual and Mutation Surveyor detection for low-level sequence variants. Further work is now underway at KGC to develop and evaluate COLD-PCR (CO-amplification-at-Lower Denaturation-temperature) to enrich low level sequence variants in somatic mosaics and in colorectal tumours.

Natalie is coming to the end of her two year supernumerary training post and, by the time this comes to print will have left KGC for a permanent position at St George's hospital in South West London. We are sorry to see her go but wish her every success at St G.

BRCA: 15 Years of Progress. The Third International Symposium on Hereditary Breast and Ovarian Cancer, Montreal, Canada, 14-16 October 2009

Joanna Campbell, GSTS Pathology, Guy's Hospital, London

The conference was organised by the Hereditary Breast and Ovarian Cancer Foundation (HBOC), a charity established in 2003 by a family in response to their experience of breast cancer and a BRCA1 mutation. Marla Miller was diagnosed with breast cancer in 2001, and was subsequently found to have a BRCA1 mutation. Her sister Joanne chose to be tested for the BRCA1 mutation and was found to be a carrier. Joanne felt empowered by the knowledge of her carrier status and opted for preventative surgery, but wished her sister had had that knowledge before she developed cancer, and hoped that there would be better preventative options available in the future for their daughters. Joanne and her husband Harley Eisman, a paediatrician at The Montreal Children's Hospital, founded the HBOC with a mission of awareness, action and research. Families at risk of carrying a BRCA mutation should be made aware and be given sufficient knowledge and resources so that they can take action, and support should be available for research into cancer treatment and prevention for BRCA mutation carriers [See "News from the Web" on BRCA Patents – Ed].

The title of the meeting related to the announcement at the American Society for Human Genetics Meeting, held in Montreal 15 years previously of the identification of the BRCA1 gene, and the general theme of the meeting was the progress that has been made since then. The majority of delegates were clinicians and genetic counsellors, but with a very strong field of presenters from many disciplines the meeting covered a broad range of topics including basic research, treatment and management of BRCA1/2 related cancers and counselling issues. There was also a one day lay conference for members of the general public, particularly aimed at those living with a BRCA1/2 mutation.

The highlight for me was a session of lectures and a special interest group concerning variants of unknown significance (VUS). Dr Fergus Couch presented an overview of using functional assays to assess VUS, Dr Sean Tavtigian showed how to combine multiple sources of evidence using a Bayesian approach to aid classification of VUS, and Dr Sharon Plon presented a classification system for VUS which is based on the probability of a variant being pathogenic, and which is linked to clinical guidelines for testing relatives and for cancer surveillance. The aim is that this classification system will be adopted world-wide to improve consistency in classification of variants and in clinical management of individuals with VUS1. This five point classification is similar to that described in the CMGS guidelines for interpreting unclassified variants, but includes an additional category of "uncertain" which from my experience is likely to contain the majority of BRCA1/2 variants we encounter.

The Special Interest Group on VUS was chaired by members of the Breast Cancer Information Core (BIC) Steering Committee, who demonstrated their method of classifying variants using examples submitted in advance by conference delegates. It was useful to see how they combined evidence about family history, co-segregation and co-occurrence to arrive at a final probability of pathogenicity for a variant that I had submitted. It was reassuring that their conclusion was the same as mine, but frustrating as it remained classified as uncertain. It was also good to hear that BIC has employed a new database curator to help keep the database up to date, and that they are hoping to convert it to HGVS nomenclature in the future which will make it easier for us to use and to submit to.

Dr Andrew Tutt presented promising results from the PARP-inhibitor trials, and there was a session covering other genes involved in an increased risk of breast cancer including CHEK2, PALB2, BRIP1, and the results of genome wide association studies. There was also a very interesting talk from Dr Steven Narod about whether there is a case for offering genetic testing outside the normal procedure of testing an affected family member with a strong family history. He presented results from two studies where genetic testing was offered via adverts in a newspaper or magazine. This identified a large number of BRCA1/2 carriers who would not otherwise have been tested as they would not fulfil current criteria. This allowed these individuals to undergo increased breast cancer screening, and to make decisions about risk reducing surgery before actually developing cancer.

This year the conference included poster presentations for the first time, and my poster summarising BRCA1/2 mutation screening in our laboratory was well received and led to a collaboration with scientists from Myriad to share information on a very rare VUS to aid classification.

I thoroughly enjoyed the meeting, and in particular the chance to get up to date with all aspects of current research into hereditary breast and ovarian cancer in a single meeting. The next meeting will be in 2011, see www.hboc.ca for more information.

I would like to thank the CMGS for awarding me a travel grant to attend this meeting.

Abstracts from the meeting have been published in Current Oncology 16(5)

1. Plon SE, Eccles DM, Easton D, Foulkes WD, Genuardi M, Greenblatt MS, Hogervorst FBL, Hoogerbrugge N, Spurdle AB, Tavtigian SV. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. *Hum Mutat* 2008; 29:1282-1291

UK NEQAS for Molecular Genetics Steering Committee

UK NEQAS
www.ukneqas-molgen.org.uk

UK NEQAS FOR MOLECULAR GENETICS
UK NATIONAL EXTERNAL QUALITY ASSESSMENT SCHEMES
CPA
Accredited EQA Scheme
Reference No: 051

Vacancies: Members of the molecular genetics profession are invited to apply to join the UK NEQAS for Molecular Genetics Steering Committee for 2010.

Remit of Steering Committee: The Steering Committee meets five times a year and is responsible for the scope and direction of the scheme whilst taking into account the needs and technological advances of the genetic testing community. Members are involved in setting performance standards and liaising with other professional bodies on quality assurance. Members provide guidance to the Scheme Organiser and are responsible for overseeing one disease EQA scheme per year. All travel expenses are reimbursed. The full responsibilities of the Steering Committee can be obtained from the Scheme Organiser.

Contact: For further details or to register your interest please contact the Scheme Organiser:

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From the Web

The Papal Phone Call

Pope Benedict XVI has made Francis Collins an offer he could not refuse and appointed him to the Pontifical Academy of Sciences, a group tasked with promoting "the progress of the mathematical, physical and natural sciences and [studying] epistemological problems," according to the Vatican's website: http://www.vatican.va/roman_curia/pontifical_academies/acdscien/ . Other members of the 80-person academy include David Baltimore, Paul Berg, and Stephen Hawking. [from GenomeWeb News]

They Cut You Off and Blame Their Genes

A small study by neurologists at UC-Irvine suggests that people with a gene variant (p.Val66Met) that limits the availability of brain-derived neurotrophic factor (BDNF) do about 20 percent worse on driving tests than people with the common variant. Previously, it had been shown that people with the variant have a smaller portion of their brain stimulated when doing a task and it is linked to slower recovery from a stroke. "We wanted to study motor behavior, something more complex than finger-tapping," says lead author Stephanie McHughen, to Scientific Blogging. "Driving seemed like a good choice because it has a learning curve and it's something most people know how to do." The study was published in Cerebral Cortex. [from GenomeWeb News]

Qiagen Acquires UK's DxS in Deal Worth up to $130M

Qiagen has announced that it has acquired Manchester diagnostics firm DxS in a deal that could be worth as much as $130 million. DxS brings to Qiagen a portfolio of molecular diagnostic assays and intellectual property, and a pipeline of active or planned companion diagnostic partnerships in oncology with several pharmaceutical companies. DxS has developed a set of molecular diagnostic assays that allow physicians to predict patients' responses to certain cancer treatments in order to make

them more effective and safer; Qiagen said that the acquisition provides it with a strong leadership position in the personalized healthcare arena.

DxS currently offers several real-time PCR tests, including a test for the mutation status of the oncogene KRAS, which is indicative for successful treatment of patients with metastatic colorectal cancer using EGFR inhibitors. This product has been CE-marked and is in current use in the UK, and is expected to be submitted for US regulatory approval in 2010.

Qiagen said that it intends to establish a Center of Excellence in Pharma Partnering at DxS' Manchester headquarters, and that it expects the location to grow in size.

Searching for Recurrent Mutations

Elaine Mardis and her colleagues at Washington University in St. Louis sequenced the genome of a man with acute myeloid leukemia using Illumina's Genome Analyzer II and identified 64 mutations, according the report in the New England Journal of Medicine. Of those, 12 were somatic mutations in coding regions and 52 were somatic point mutations in conserved or regulatory regions. Four of the mutations also occurred in at least one other AML sample that had also been tested and two of these were already known mutations. In a statement, senior author Timothy Ley says, "Only by sequencing complete genomes of cancer patients are we going to find unexpected, recurring genetic mutations that are highly likely to be important for cancer to develop and grow." [from GenomeWeb Daily News]

Court Denies Motion to Dismiss BRCA Patent Suit Against Myriad, Others

A US district court has denied a motion by the US Patent and Trademark Office (USPTO), Myriad Genetics, and the University of Utah Research Foundation (UURF) to dismiss a lawsuit brought against them challenging the legality and constitutionality of BRCA gene patents owned by the University of Utah and exclusively licensed to Myriad.

In a decision handed down recently, the US District Court for the Southern District of New York determined that the plaintiffs, led by the Association for Molecular Pathology, "possess the necessary standing to bring their claims against the defendants," and that the facts alleged in the case "are plausible, specific, and form a sufficient basis for [the] plaintiff's legal arguments."

The plaintiffs originally filed suit against the USPTO, Myriad, and the UURF in May, claiming that the BRCA gene patents "stifle research that could lead to cures and limit women's options regarding their medical care."

UURF has exclusively licensed the rights to perform diagnostic tests on the genes to Myriad, which provides genetic testing for ovarian and breast cancer. Myriad also is co-owner of several patents challenged in the suit. In total, the plaintiffs are challenging the legality and constitutionality of four categories of claims in seven US patents.

In July, the USPTO filed a motion to dismiss the case, arguing that the "plaintiffs lack standing to sue the USPTO, the Court lacks subject matter jurisdiction, and the action is barred by the sovereign immunity. Moreover, plaintiffs' unsupported legal conclusions fail to state a claim for a constitutional violation and therefore should be dismissed."

The lawsuit has essentially been viewed as a challenge to the entire practice of gene patenting, and the outcome of the case could have far-reaching effects for the research and genetic diagnostics fields [from GenomeWeb News].

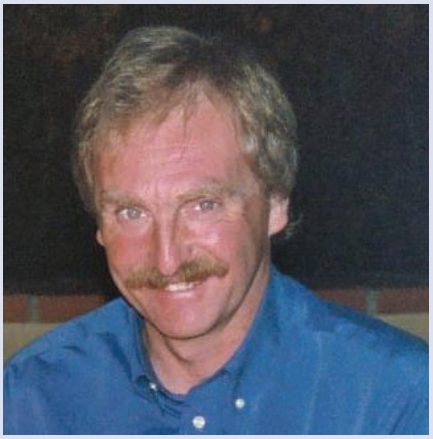
By the time this comes to press, the plaintiffs' reply should have been submitted and the hearing held.

The Broad Institute buys 30 new Illumina 'Genome Analyzer' systems

See:
http://www.broadinstitute.org/about/history.html

Finally, we should not forget the difficulties faced by colleagues in the 'new' developing European countries, such as Romania, where the burden of PKU on the health service is significant:
http://www.orpha.net/actor/EuropaNews/2009/090729.html#16159

CMGS News Editor



Deadline for contributions for next issue is 30 April 2010

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Editorial

As we approach the end of the first decade of the new millennium, it seems a good time to reflect on the enormous changes that have taken place in the field of cancer genetics since 2000. The progress of advances in technology, knowledge and understanding of the genetic basis of cancer is exciting and inspiring. In my view, two presentations at the CGG winter meeting in November particularly highlighted these advances and the challenges they bring: Caroline Ogilvie gave an eloquent and thought provoking presentation on CGH array testing and the implications for cancer genetics and Paul Pharoah updated us on the role of SNPs and raised the issue of targeting the age of commencing breast screening in the general population. The lead article in this section of the newsletter by Rebecca Brown and colleagues from Leeds gives details of another development in the establishment of a diagnostic service for malignant melanoma (CDKN2A/CDK4). Julian Adlard has kindly provided a comprehensive summary of the talks I have mentioned, amongst others, in his article about the November meeting.

Interpreting the advances in technology and explaining this to patients is a challenge in itself. Gillian Crawford and Charlotte Dubras have described their experience of running a BRCA patient day in Southampton and Debbie Marsden and colleagues have given an account of an initiative for involving patients in designing and developing research in Wales. Gareth Evans has updated us on progress with the Short Clinical Guideline for NICE which will hopefully help to move screening forward for women with breast cancer. These three articles demonstrate that communicating with patients remains at the heart of the work we do.

The report from Anneke Lucassen, Chair of the CGG, provides an update on the changes in the CGG steering group and is a reminder about the next meeting in Amsterdam in Spring 2010. As Anneke has mentioned, this is my last editorial as newsletter editor and I would like to take this opportunity to thank everyone who has responded to my (sometimes) desperate requests for articles over the last few years, not least those who have contributed to this edition. I hope you will continue to support Emma Woodward who will be taking over as editor from the next newsletter. Emma's email address is e.r.woodward@bham.ac.uk

Just as the field of cancer genetics has grown over the past ten years, so too has membership of the CGG. At the last steering group meeting Gareth reminded us of the early days of Cancer Family Study Group which some of you may recall preceded the CGG. The CFSG had a small (but select) membership and the meetings were similarly small, providing an opportunity for researchers to share ideas at a time when all cancer genetics was undertaken in a research setting. The size of the November meeting and the nature and quality of the presentations is a reflection on how far cancer genetics and the CGG have come in the last ten years. I wonder where we will be in 2020…

Chris Jacobs

Report from the Chair

Anneke Lucassen

It's hard to believe I've entered my second year as Chair of CGG - doesn't time fly when you are having fun….or getting older! Of course having Gareth as retiring chair makes it all seamless, so thank you Gareth.

CGG has had another busy and successful year. Both the 2009 national meetings were very well attended and financially our coffers look healthy, which is remarkable in the current climate. Thanks to Ian Ellis for keeping the balance sheet looking good. Sadly, our secretary, Gabriella Pichert, has been lured back to her native Switzerland and will therefore retire from her post early in 2010. We will miss her. Emma Woodward will take over the newsletter editorship from Chris Jacobs over the next year, though Chris has kindly agreed to an overlap period to show her the ropes. Thanks Chris for all your efforts in filling the CGG pages with interesting articles.

Our annual two-day meeting this year was in Glasgow in May. Steering group member, Nicola Bradshaw and her colleagues coordinated an excellent programme of high quality talks as well as a ceilidh and conference dinner in between the two days to keep us going. We now need volunteer hosts for the spring 2011 meeting, so do please get in touch if you might like to do this.

Our winter meeting is usually a one day research update, but this year we extended this to a two day meeting held jointly with ABS (Association of Breast Surgery) and BASO ~ ACS (British Association of Surgical Oncologists ~ Association for Cancer Surgery) at the Royal College of Surgeons at Lincoln's Inn Fields London. This meant that the costs of the meeting were somewhat greater than usual. In an attempt to offset some of the costs for non-consultant CGG members, we offered 70 fifty-pound bursaries on a first come first served basis. The interim report from our treasurer suggests that all who applied received a bursary.

Next year we are looking forward to a double joint meeting in the zoo in Amsterdam! Both Dutch CGG and CGS will have overlapping meetings with UK CGG and CGS. The CGG meeting will be on 10 and 11 March, with the 11 March being the joint day with CGS, of which the main theme will be cancer dysmorphology syndromes. The call for papers has just come out, with a closing date of January, so get your abstract pens out!

Because of BSHG's recent reminder about the highlights section, asking about members' publications, I thought I would use this space to let readers know about a special issue of Familial Cancer, due out in early 2010. Tara Clancy and I edited this issue, and many of the papers were peer reviewed by CGG members (thank you so much to all who did this behind-the-scenes important task). The issue brings together 14 papers (all of which are already published on line and available at: http://www.springerlink.com/content/105711/?Content+Status=Accepted) exploring the issues around genetic testing during childhood. Although many focus on the issue from a cancer perspective, there is also a more general discussion of the ethical and legal issues involved. For example, Ainsley Newson and Sam Leonard consider the ethical issues raised by pre-adoption predictive genetic testing for cancer and argue that under a principle of consistency, testing of this kind should be discouraged if the same test would not be offered for a child who is not being placed for adoption. Robert Wheeler explores the legal aspects of such a case that was tested under a court order. Mike Parker gives an overview of the types of cases involving predictive genetic testing in childhood that have been discussed at Genethics Club (www.genethicsclub.org) over the past 8 years. Gareth Evans and colleagues and Gill Crawford provide case reports illustrating difficulties in practice. Angus Clarke argues that we are right to have guidelines urging caution for such testing, whilst Angela Fenwick questions whether guidelines might lead to tick box behaviour rather than case by case assessments. Pascal Borry and colleagues look at companies' attitudes to testing of minors for direct to consumer testing, whilst Suzanne O'Neill explores primary care opinions about BRCA1/2 testing in minors. Beth Peshkin has developed a decision support intervention for mothers undergoing BRCA1/2 testing and to facilitate communication with their daughters. Roy Gilbar compares the legal perspectives on Consent, Communication of Information and Confidentiality in different countries and Tara Clancy reviews the ethical issues in prenatal diagnosis and preimplantation genetic diagnosis for later onset inherited cancer predispositions. Jonathan Montgomery and I summarise the state of play with professional guidance in the area. The 1994 CGS guidance is in the process of being updated and rebadged as BSHG guidance and will argue for a 'presumption of caution' (for tests that incur no immediate medical benefit or management issues), rather than a prohibition of testing in childhood.

It's interesting, that whilst there are nearly 30 national and international guidelines that state that genetic testing in childhood for adult onset conditions should be deferred (so that children can decide for themselves at a future date), this issue continues to arise in clinical practice. But guidance does not prescribe what should be done in all cases, and engaging parents in a discussion about the pros and cons of testing is more likely to result in a mutually satisfactory outcome, than telling parents that guidelines prohibit testing of their child.

New UKGTN services offered in Leeds

Rebecca Brown, Claire Bosomworth, Jenny Simmonds, Rachel Robinson, Ruth Charlton

Familial Cancer- special issue on genetic testing in childhood

Predictive genetic testing in children: Where are we now? - an overview and a UK perspective	Anneke Lucassen and Jonathan Montgomery
Health-related direct-to-consumer genetic testing. A review of companies' policies with regard to genetic testing in minors	Pascal Borry, Heidi C Howard; Karine Sénécal; Denise Avard,
Primary Care Providers' Willingness to Recommend BRCA1/2 Testing to Adolescents	Suzanne O'Neill; Beth N Peshkin; George Luta; Anisha Abraham; Leslie Walker; Kenneth P Tercyak
On the development of a decision support intervention for mothers undergoing BRCA1/2 cancer genetic testing regarding communicating test results to their children	Beth N Peshkin; Tiffani A DeMarco; Kenneth P Tercyak
Genetic Testing of Children for Familial Cancers: A Comparative Legal Perspective on Consent, Communication of Information and Confidentiality	Roy Gilbar,
Childhood predictive genetic testing for Li-Fraumeni syndrome	D Gareth R Evans; Peter Lunt; Tara Clancy; Rosalind Eeles
Opinion Piece. Predictive testing for pre-malignancy as a prelude to adoption? An English case.	Robert Wheeler
Childhood genetic testing for familial cancer: should adoption make a difference?	Ainsley J. Newson and Samantha Leonard
A clinical perspective on ethical arguments around prenatal diagnosis and preimplantation genetic diagnosis for later onset inherited cancer predispositions	Tara Clancy
The challenge of developmentally appropriate care: Predictive genetic testing in young people for familial adenomatous polyposis (FAP)	Rony E Duncan; Lynn Gillam, Julian Savulescu, Robert Williamson, John G Rogers,; Martin B Delatycki,
Genetic testing in children and young people	Michael Parker,
Are guidelines for genetic testing of children necessary?	Angela Fenwick,
What is at stake in the predictive genetic testing of children?	Angus J Clarke,
Predictive genetic testing in a young child: a case report	Gillian Crawford and Anneke Lucassen,

In May this year gene dossiers were submitted for consideration by the UKGTN for malignant melanoma (CDKN2A/CDK4) and Lynch syndrome (PMS2) analysis and were successfully accepted by the group.

A diagnostic service for malignant melanoma (OMIM 155600) has been developed in collaboration with Prof Julia Newton Bishop's research group. Initially confirming findings from the research laboratory, this service now enables comprehensive sequence analysis of the CDKN2A gene which encodes p16/INK4a and p14/ARF and targeted sequence analysis of exon 2 of the CDK4 gene. MLPA gene dosage analysis is currently under development and will enable detection of deletions at 9p21.

The estimated incidence of melanoma in the UK is ~10 cases per 100, 000 per annum. This service aims to target familial melanoma cases ie, individuals from families with three or more cases of melanoma; individuals from families with two cases of melanoma in first degree relatives, with multiple primary melanoma in at least one case; or individuals from families with one case of melanoma and pancreatic cancer in a first degree relative. It has been estimated that between 25-50% of familial melanoma kindreds are affected by a CDKN2A mutation, prevalence increasing as the number of affected individuals increase in the index family. An overall worldwide prevalence was estimated at 39% by the melanoma genetics consortium (GenoMEL), reflecting geographical differences. In a small number of melanoma prone families, codon 24 in exon 2 of the CDK4 gene is mutated. Mutation penetrance has also been shown to be influenced by geographical location and likely differences in UV exposure.

Detection of a mutation in a high risk family enables planning of long term surveillance and possible participation in pancreatic cancer research programmes, whilst a negative test in a mutation positive family would normally lead to discharge from clinical follow-up following education on self examination and sun protection. Since January this year 48 samples have been processed by our laboratory, 10 confirmation tests of research findings, 26 predictive and 11 diagnostic tests. Of the diagnostic screens a CDKN2A or CDK4 mutation was detected in three patients (27%).

PMS2 gene analysis has been available in our laboratory since 2007. Heterozygous germline mutations have been identified in cases of Lynch syndrome with ~2-5% of colorectal cancers in the UK being attributable to Lynch syndrome (OMIM 120435; 114500). Homozygous or compound heterozygous germline mutations have also been implicated in severe childhood cancers with an apparent recessive inheritance pattern. Clinical evidence indicates that the penetrance of PMS2 mutations is incomplete and lower than the commonly investigated HNPCC genes (MLH1, MSH2, MSH6), although an exact figure has not been established. Patients are generally selected for analysis according to local criteria of either: families with a history of colorectal cancer where immunohistological analysis has identified loss of PMS2 expression alone, or combined loss of PMS2 and MLH1, with no mutations identified in MLH1, or families with a history of colorectal cancer where tumour tissue displays microsatellite instability and no mutations have been identified in MLH1, MSH2 or MSH6.

PMS2 on chromosome 7p22 has 15 exons and encodes the DNA mismatch repair gene similar to E coli mutL, which in it's active form functions as a heterodimer with MLH1. Loss of MLH1 or PMS2 expression results in defective mismatch repair. Molecular analysis is complicated by the fact that 15 PMS2 pseudogenes (Y) have been identified, 14 on chromosome 7q containing pseudocopies of some or all of exons 1 to 5, with a fifteenth, PMS2CL(Y0), containing exons 9 and 11-15, also residing on 7p22. This has lead to concerns that early investigations may have failed to detect pathogenic mutations, or misinterpreted the pathogenicity of variants occurring within pseudogene affected exons (see figure below).

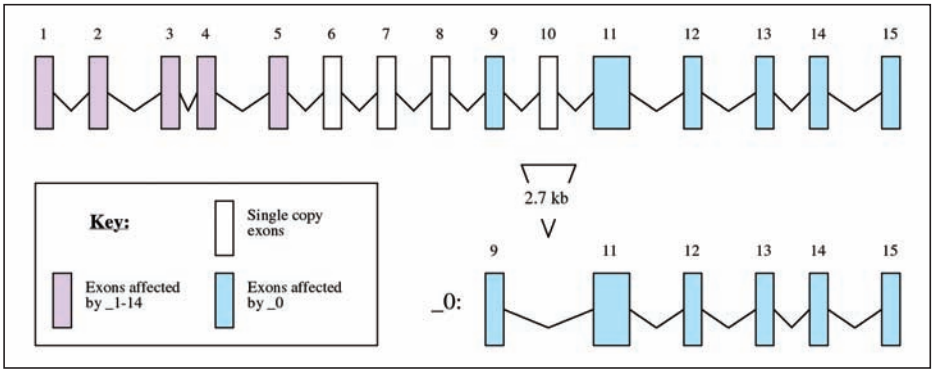

Figure: Schematic representation of PMS2 and exons affected by pseudogene sequence

We offer testing of exons 1-10 by sequence analysis, long range PCR followed by PCR and sequencing of exons 11 and 12, MLPA gene dosage analysis of exons 1, 2, 5 to 12. Exons 13 to 15 are not analysed due to the inability to select for gene specific rather than pseudogenic PMS2 sequence. Analysis to date has detected pathogenic mutations in 48% patients investigated (n=64). Where immunohistochemical data have been available, the majority of mutations (80%) have been identified in patients (n=30) with isolated loss of PMS2 expression, with none identified in patients (n=20) where both MLH1 and PMS2 expression is lost. Locally we are working towards including PMS2 testing recommendations within the HNPCC best practice guidelines, which are currently being updated by the CMGS.

Please consult our web site for further information regarding molecular screening on offer in our laboratory (http://www.leedsth.nhs.uk/sites/leedsdna/Genetictests.php).

Short guideline on women affected with breast cancer and a family history

Gareth Evans

In the last edition of the newsletter, we drew your attention to the potential gap in NICE guidance that had occurred after publication of the early and locally advanced (CG80) last November. This guideline stated that women affected with breast cancer who had a family history of the disease were covered by the familial breast cancer guideline (CG41). However, CG41 specifically excluded affected women. A letter from the chair persons of BSHG, CGS and CGG was written to NICE with concerns over the lack of guidance to inform management of the contralateral breast (surgery and MRI) for women with a family history. Professor Gareth Evans wrote a case for a short guideline, which went out for consultation last Spring. After the consultation period he was called into Prof Richards' Committee to present the needs for the short guideline. The application received high scores and has now gone forward to the final selection process, but still faces stiff competition from other applications. Although some of us are now able to get MRI screening for affected women with mutations, this may become harder after the NHSBSP takes over responsibility for familial screening next year. Prof Julietta Patnick has presented the current plans which starts with piloting the moderate risk mammography aged 40-49 years and high risk MRI screening in South West London and Southampton. Absence of NICE guidance for affected women may make it difficult to obtain screening through the NHSBSP.

Patient centered initiatives at the Cancer Genetics Service for Wales

Marsden D, Iredale R and Murray A

The Cancer Genetics Service for Wales (CGSW) was established in 1998 for people across Wales with concerns about their family history of cancer. We are in the middle of a 5-year programme of work focusing on patient centeredness in service development and delivery. We began with a series of Patient Open Days across Wales in 2008 and in Autumn 2009 we recruited 169 patients to Patient Panels in Cardiff, Swansea and North Wales. Each Patient Panel had 3 tasks: reviewing the Family History Questionnaire used at CGSW; creating the StoryBank and making suggestions for CGSW to better improve the long-term information and support needs of people living at risk of inherited cancer.

Initiatives for 2010 include developing the StoryBank and e-genetics projects in collaboration with patients. The purpose of the StoryBank is to collect stories (n=20) about living with the risk of inherited cancer. Patients describe their journey through CGSW from the point of referral through to living with risk on a long-term basis. Some stories come from individuals; others are compiled by groups of patients attending workshops. All of the stories will be available on the CGSW website (e-genetics) in a variety of forms, including text-based, sound only and video. The intention is to provide information and support to new and existing patients; to showcase good practice in cancer care and to continually involve patients in our service development in order to deliver better cancer genetics services in Wales.

The inaugural meeting for Wessex BRCA carriers

Gillian Crawford and Charlotte Dubras

We have 344 individuals with a BRCA mutation on our database. The cancer genetics team felt that some carriers might welcome the opportunity to meet together for both information and support. On Saturday 14 November 2009 the Wessex Clinical Genetics Service held its first meeting.

Scoping exercise

Prior to organising a meeting we completed a scoping exercise asking a small group of carriers for their views. We sent out 48 questionnaires and received 19 responses, of which 14 were interested in an event being organised. The questionnaire asked their views on timing of the event (weekday evening or Saturday), venue (hospital or non-hospital venue) and interest in being involved in a support group in the future. The questionnaire also gave a list of topics and asked respondents to indicate which they would like see included in the day (for example, screening, risk reduction surgery, cancer treatments, how to share information with families and children and insurance updates). We also asked for their suggestions. The questionnaire indicated a general support for the meeting and the responses formed the basis of the programme. We secured £500 from Macmillan to set up the meeting and spent £400 of this on refreshments, postage etc. There was no charge for delegates to attend.

The day itself

Three hundred and twenty invitations were sent out with a total of 156 replies. Thirty-two people indicated that although they were unable to make this date they would like to attend a future meeting. We had a total of 89 participants (very good attendance as there was atrocious weather

A report from the CGG joint scientific conference with ABS & BASO~ACS Royal College of Surgeons, London, 23-24 November 2009

Julian Adlard

on the day, with the Isle of Wight ferry being cancelled and a postal strike in the run up). We held it in a local hotel that donated the room free of charge. Participants were able to bring one guest with them but many attended alone. The programme on the day included a genetic refresher, management options for BRCA carriers (the content of this session was planned in response to the questions we received from participants on their reply slip). There was also a session on sharing test results in the family, which was interactive with small group work. Individuals shared their experiences and talked through strategies they had found helpful when sharing results. Despite our reservations that participants may not want to engage in a group discussion, it proved difficult to stop them chatting. We had an extended question and answer session that included questions ranging from vasectomy to HRT. Informal discussions took place at two coffee breaks and many carried on chatting after the programme had finished.

Feedback

Fifty-two evaluation forms were completed with only one person saying they would not come to a future meeting. The talks and small group feedback will be put on our departmental website for participants to access and also those who could not attend. A number of individuals offered to move plans forward for a support group and we have set a date for a further meeting next year.

Perhaps the success of the day is best summed up by one participant who approached us in Frankie and Benny's, where the cancer genetics team were having lunch, to shake our hands and thank us for putting on a great morning!

The CGG Winter meeting was held at a joint conference with the Association for Cancer Surgery and Association of Breast Surgery at BASO. Abstracts for poster presentations and some of the lectures can be found in the European Journal of Surgery 2009: 35(11); 1200-1242.

Results of the FH01 study, assessing mammographic screening of women aged 40-49 at increased risk were presented by Stephen Duffy. Six thousand, six hundred and sixty nine women were recruited, who had undergone 22360 mammographic episodes. One hundred and twenty five breast cancers were identified of which 33 (26%) were carcinoma in situ and 20 (16%) were interval cancers not detected by the screening. The size, grade and nodal status of the cancers in FH01 compared favourably with other trial series (Age/Dutch studies). Predicted 10-year survival using the Nottingham prognostic index for FH01 affected cases was 84% compared with ~75% in the other series. Consideration is being given about how best to factor the DCIS cases into the analysis. It is hoped that updated results will be published in the Lancet.

Gareth Evans reported results of several studies, including ongoing progress of FH02, assessing mammographic screening in women aged 35-39 at increased risk. This study is continuing to recruit and is funded by Breast Cancer Campaign for three years. The controls/relatives from the POSH study may be used as a comparison group in the analysis. Further results from MARIBS including anonymous BRCA testing appeared to strengthen the case for MRI screening of BRCA carriers relative to those without identified mutations. These data raised the merits of testing unaffected family members from high-risk families where all affected relatives are deceased. Results of economic modelling suggested that BRCA testing below a 10% threshold (equating to 15-19 points on the Manchester score) would be very expensive in terms of cost-effectiveness, but between 10-20% may be more acceptable.

The Cancer Reform Strategy has set out several changes to breast cancer screening, including extending the National Breast Screening Programme (NHSBSP) to include women from age 47-73, increased use of digital mammography, and transfer of family history screening (including MRI) to the NHSBSP. Julietta Patnick gave an update on progress with implementation. Demonstration projects are being developed in Leeds, SW London and Southampton. Conversion to digital mammography has been slower than anticipated. The NHSBSP does not intend to perform risk assessment and this will remain with family history clinics and genetics services. An important unresolved question is whether any mammographic screening under the age of 40, or more frequently than three yearly from age 50, which is currently offered by some services, will be available via the NHSBSP.

Genome-wide association studies (GWAS) have identified 13-18 low penetrance breast cancer susceptibility alleles associated with relative risks of around 1.1. Paul Pharoah gave an interesting lecture on how these alleles could be used in practice. Even in combination, this genotyping is little better than chance at predicting outcomes for an individual woman. However, low penetrance alleles could be used to modify the starting age of breast screening, with earlier or later screening depending on the results of SNP testing, perhaps combined with non-genetic modifying factors. This would help to ensure that women were having screening at equivalent levels of risk.

Diana Eccles presented data from the POSH study showing 10/11 (91%) breast cancers in patients with Li Fraumeni syndrome were HER2 positive, suggesting a possible histopathological phenotypic association. It is proposed to validate these findings as part of the planned COPE study. Carlos Caldos summarised the current knowledge of the molecular taxonomy of breast cancer, including the reminder that not all triple receptor negative (TNT) breast cancers are of basal type. If pathology laboratories routinely performed immunohistochemistry (IHC) for basal cytokeratins and EGFR this would lead to better definition of molecular subtypes.

Adam Rosenthal presented ovarian screening results from Phase I of UKFOCSS. 3563 women were recruited with 11366 screening years of follow-up. Nine prevalent cancers were identified on the first screen, with a further 12 incident cancers on follow-up screening, and four interval cancers. One third were stage I/II at diagnosis, and the majority of cancers identified were in confirmed mutation carriers. Phase 2 is continuing to recruit and the steering committee are due to meet again in March 2010 to decide whether to close recruitment at the end of that month. Screening of trial participants will continue for several years. However, it remains unclear what, if any, screening will be available around the country to other women at increased risk after closure of UKFOCSS. The study coordinators propose to send a questionnaire to participating centres to investigate this further.

Tim Rebbeck gave a comprehensive overview of risk-reducing bilateral salpingo-ophorectomy (BSO). Results from PsyFOCS showed that the most common reason to withdraw from UKFOCSS is the decision to have BSO, prompted particularly by positive genetic testing or by recall after equivocal screening results.

Early data from the IMPACT study of prostate cancer screening for BRCA carriers aged 40-69 was reported. IMPACT is open in 33 centres in 10 countries. Target recruitment is 500 BRCA1 carriers, 350 BRCA2 carriers and 850 controls. Current recruitment was reported to be 734, with relatively more controls than cases required. ~60 men have so far had a PSA >3, with 43 having had a biopsy, and 17 diagnosed with cancer, most of which have been of high grade. The PPV of a PSA >3 in IMPACT is ~40% compared with 24% in the ERSPC population-based trial.

The Ernest Miles lecture was given by Robin Phillips from St Mark's and was an excellent summary of the current management of FAP, including desmoid disease and small bowel polyposis. Lucy Side presented encouraging early results from an annual outpatient hysteroscopy screening program for women with Amsterdam II positive family histories. Nicola Cartwright reported good recruitment to the COGS2 study which is assessing environmental and genetic modifiers in MMR gene carriers. The 'difficult cases' session prompted discussion about germline methylation testing for patients with colorectal cancers showing loss of MLH1 expression and negative gene screening, particularly where the IHC had apparently 'failed' ie, normal tissue also not stained.

Caroline Ogilvie from Guy's gave a thought-provoking talk on some of the issues that may face cancer geneticists as CGH microarrays begin to replace conventional karyotyping. The Cancer Genome Project has identified about 471 genes (~1.4%) that may be linked with cancer. CGH may identify unexpected copy number gains or losses in regions encompassing recognised cancer predisposition genes. A recent study identified these at a rate of about 1 in 500 tests (Adams, SA. Genet Med 2009:11(5); 314-22). Parents with a child undergoing CGH for congenital or developmental problems may find themselves presented with additional concerns they had not expected. Colleagues arranging the tests should be advised to counsel regarding unexpected results. The Guy's team are developing a 'cancer gene watch list' for specific genes that would be included on the laboratory report if involved.

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Deadline for contributions for next issue is 30 April 2010

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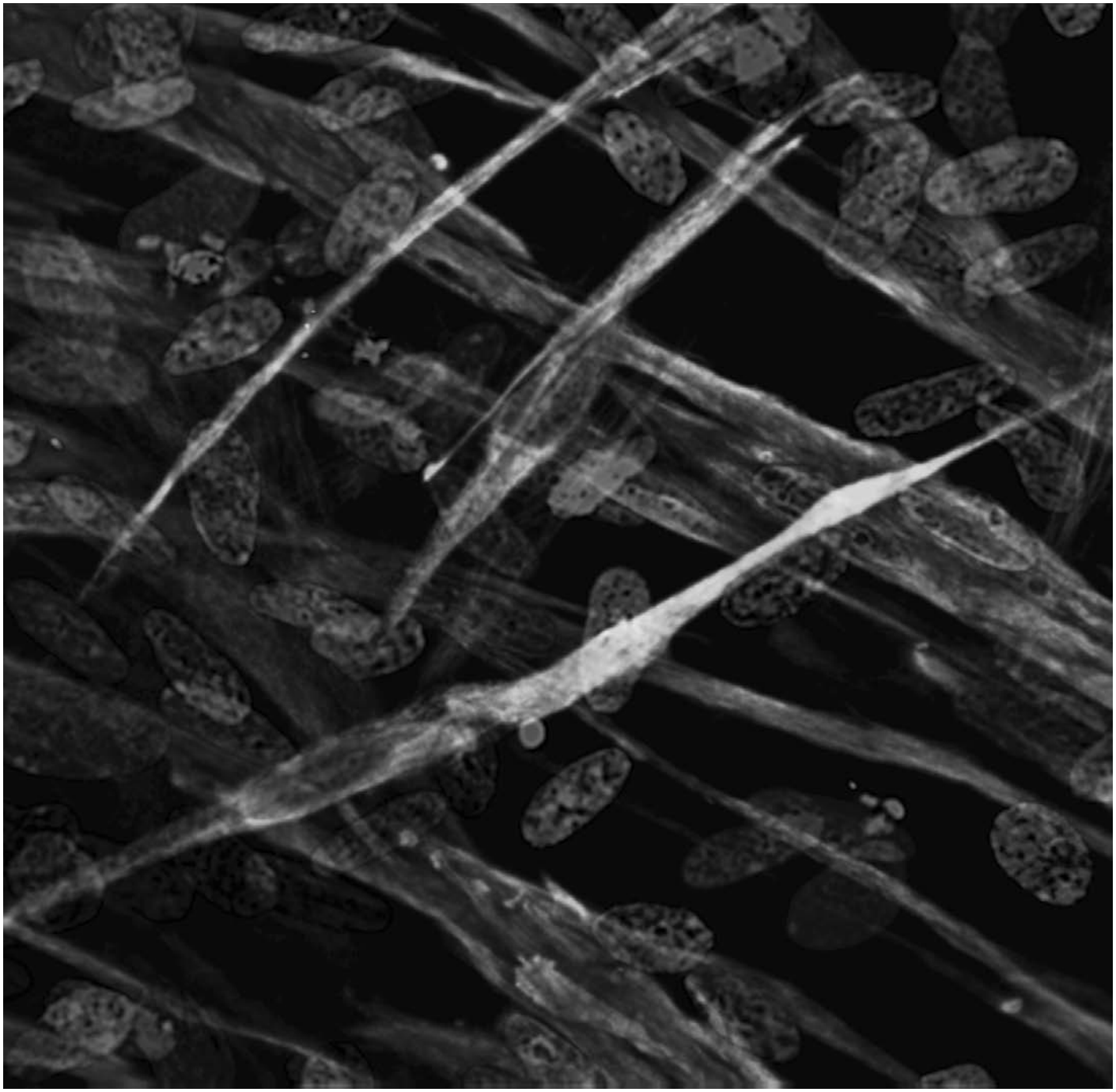

Image courtesy of Genetix Corp.