

BSGM News

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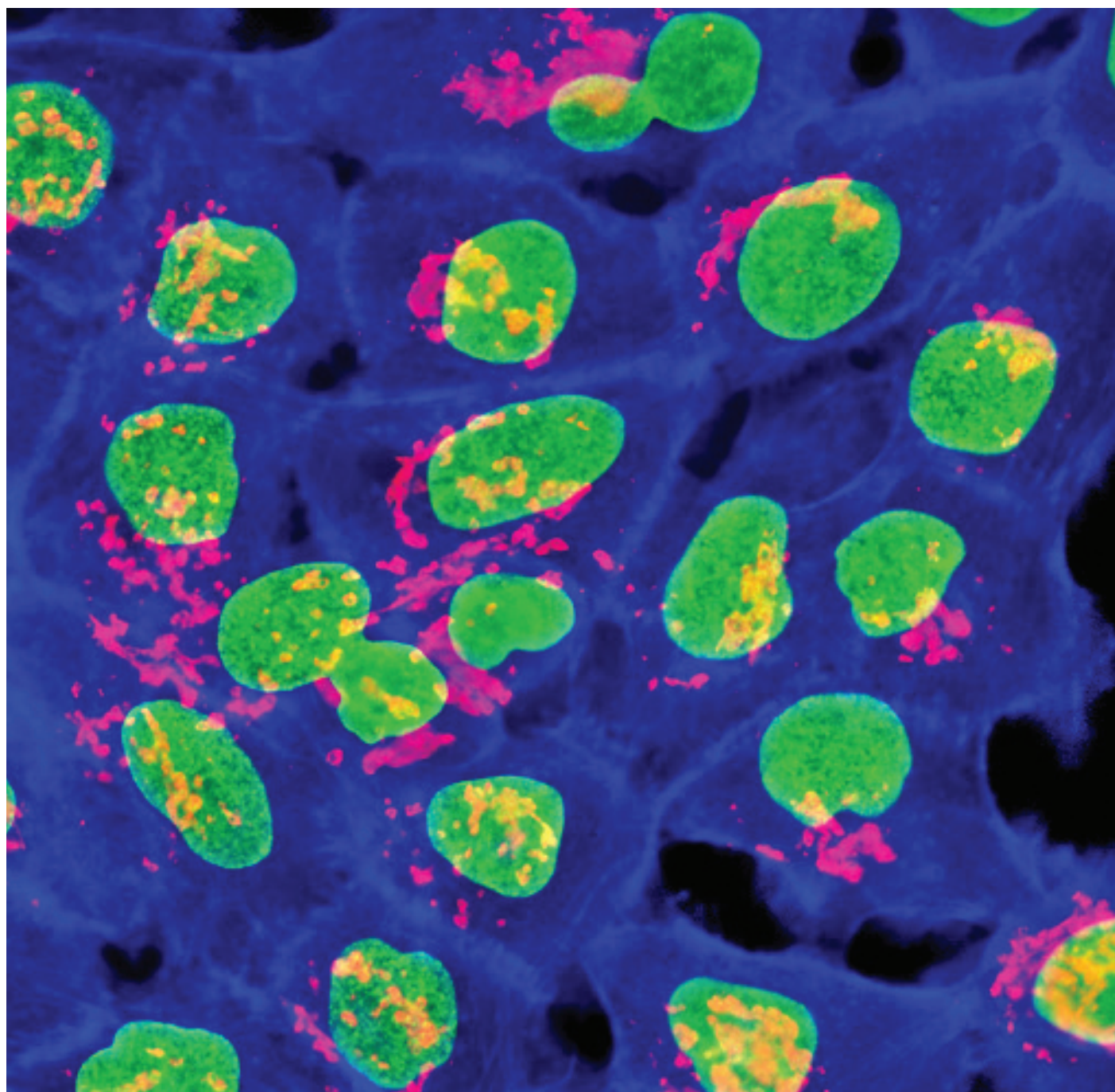
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From the newsletter editor

Welcome to the latest issue of BSGM News. While we have never previously had a themed issue of this newsletter, this could be classified as the 'genomics issue' with many articles in the main section of the newsletter describing different aspects of genomic medicine. This theme also carries through to the newsletters of the constituent groups describing how different aspects of our membership will be involved in genomics now and in the future.

Our lead article in this issue provides a summary of the PHG Foundation's report *Realising Genomics in Clinical Practice*. The findings from this report are timely as many members of the BSGM are involved with various aspects of the 100,000 Genomes Project and as such will need to consider the many varied and often challenging ethical, legal and social implications of implementing whole genome sequencing in both a clinical and research setting.

This issue also contains the first, of hopefully many, short articles from the newly formed special interest group – *Dermatogenetics*. This group held its inaugural meeting at the 2014 BSGM Annual conference and I would encourage any BSGM member with an interest in this area to consider joining this special interest group.

Finally, as this newsletter is for the BSGM membership, we rely on you to identify topics that may be of interest to the entire membership. If you have any ideas for future articles or features, please get in touch. My details can be found at the end of the main section.

Michelle Bishop



Chair's Report

Angela Douglas, Chairman, BSGM

Firstly, it was great to be able to host the BSGM Annual Conference in Liverpool and share the delights of my home City with all who attended. Liverpool is a great City, not only of culture; but also of heritage and science, which are at the heart of the City. The conference was scientifically an overwhelming success, thanks to the excellent organisational skills of the Scientific Committee and to Dina and the BSGM conference committee. The scientific sessions were packed with state of the art science and the opening session on Genomics set the bar high for the rest of the Conference. The Session from Health Education England gave us much food for thought and Professor Sue Hill was extremely attentive to the concerns from the audience about the workforce issues that are being faced by every workforce group in Genetics, with a promise that if we provided the evidence, Professor Hill would support the profession in finding the solutions.

The conference seems like a long time ago now and since then most of us have been engaged with the Genomics England Invitation to Tender for the positions of NHS Genomic Medicine Centres. The deadlines have been short and many, and as the days have become shorter the working week for many of us has become longer in an attempt to provide the information that would secure the ultimate goal of being one of the GMCs recruiting to the 100K Genome Project. And as if that has not been enough to occupy the day job, we have in the background kept a glancing eye out for the NHS Genetic Services reconfiguration, that has been morphed into the NHS Genomic Services Redesign, with of course no link to the GMCs.....only time will tell. At the time of

writing we still have not had sight of the Specification for the Genomic Laboratories Redesign, that was due to go out to consultation in October. NHS England's Specialised Commissioning Group sent out the following in September 2014:

"The NHS Genomics Laboratory Service Redesign Project has, in line with procurement practice in the NHS, advertised the project to the wider market for providers to register potential interest. This is a standard way to test the appetite in the market for NHS services. This process is called the Prior Information Notice (PIN). It does in no way preclude providers who do not register at this stage the opportunity to compete further in the process when the formal Invitation to Tender is issued. The next stages for this Project is

- The commencement of the 3 month public consultation on the service specification in early October
- Provider Engagement Event – November
- Issue of ITT – January 2015"

This was followed by the NHS England Commissioning Intentions published this October, stating:

"Genomic and genetic services
NHS England is currently completing preparations to carry out a formal procurement exercise to support the establishment of a stronger, more responsive, modernised and efficient genetic laboratory service. This will provide a new configuration of Central Genomic Laboratories and will affect both current regional, local and speciality-based genetic laboratory services. A public consultation, clarifying the scope

Realising Genomics in Clinical Practice

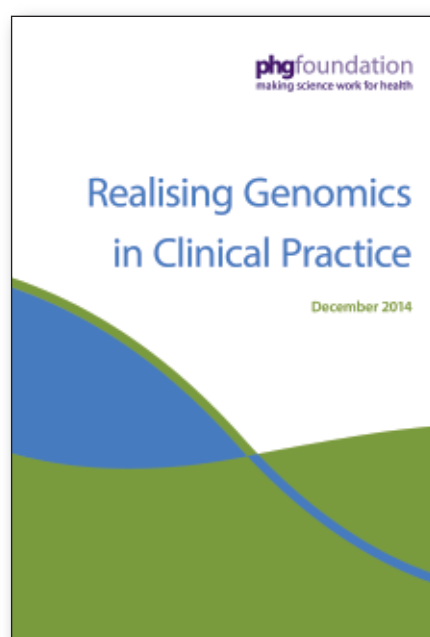
Corinna Alberg, PHG Foundation

and draft service specification requirements of the new service, will begin in the autumn. It is anticipated that the new pattern of service delivery will be in place in 2016, with a current planned 'go live' date of January 2016. NHS England is exploring the potential to use the prime contractor model to commission the tests for which NHS England is responsible via the selected Central Genomic Laboratories.

NHS England is a key delivery partner in the Department of Health-led 100,000 genome project. NHS England is currently inviting applications from providers wishing to act as NHS Genomic Medicine Centres, which will help identify suitable patients wishing to consent to participate in the project and provide sample DNA to be sequenced as part of this important national development programme."

We await the consultation release and the new specification and will involve our members in our response when that does finally happen.

Finally, I would like to take this opportunity to wish everyone a prosperous new year.



New genomic sequencing technologies have the potential to revolutionise the diagnosis and treatment of many disorders. The NHS is now on the cusp of introducing next generation sequencing (NGS) diagnostic tests, including whole exome sequencing (WES) and ultimately, whole genome sequencing (WGS). Together these technologies will form an important addition to existing genetic testing strategies, promising faster diagnosis of inherited and *de novo* diseases. The technologies will be particularly beneficial where simultaneous investigation of multiple genes is required, resulting in lower sequencing costs per gene.

But the investigation of the whole exome or genome brings significant challenges as we attempt to make sense of the huge amount of undifferentiated data these technologies generate and understand the health impact of the vast range of genomic variants –

- The identification of incidental findings (IFs) will raise questions about their interpretation and disclosure. Patients must be prepared for this eventuality through discussion as part of an effective consent process.
- Variants of unknown significance (VUS) will require clinical and laboratory expertise and time to interpret. As the significance of many of these variants becomes known clinicians will need to decide whether to re-examine sequence data and recontact patients with clinically relevant new information.

The PHG Foundation's report *Realising Genomics in Clinical Practice* aims to inform the optimal implementation of these technologies and proposes a comprehensive set of recommendations for implementing NGS/WGS/WES in ways that improve healthcare while minimising potential harms. It sets out the broad range of ethical, legal and social implications (ELSI) and practical challenges that will arise from using targeted sequencing using selected gene lists and genome-wide sequencing technologies within a clinical setting.

Background to the *Realising Genomics* project

The *Realising Genomics* project took place between 2013- 2014 and comprised of five iterative workshops engaging with a wide range of stakeholders and international experts. The resultant recommendations aim to address the ELSI challenges and resolve some of the outstanding policy issues including:

- The blurring of the interface between clinical care and research as a rapidly growing knowledge-base is populated by both activities and increasing

“A recurring theme concerned the volume of findings that might be generated”

numbers of patients cross the clinical/research boundary

- Likely changes to the patient pathway as these technologies become entrenched in clinical care and how consent, disclosure of results and various technical aspects should be managed to optimise their effective clinical implementation
- Developing a framework for implementing these technologies using gene lists as a first-line approach.

Summary of key findings

We have identified the recommendations that need be implemented in order for new diagnostic services using genomic sequencing to be implemented and delivered in an equitable and ethical manner. We have also identified a set of recommendations that should be implemented in order to deliver these technologies in the most efficient manner. The recommendations are also considered in terms of the ethical principles of beneficence, non-maleficence, autonomy and justice.

We recommend restricting the implementation of novel NGS diagnostic technologies to deliberately target analysis and interpretation to those genes associated with the patient's presenting phenotype. This can be done through developing gene lists based on phenotype. Using this approach as a first-line test, before analysing and interpreting the whole exome or genome, will help avoid large volumes of data which have adverse or unpredictable impact.

To support the interpretation of pathogenicity of genetic variants from NHS patients, an NHS Database needs to

be set up. Mandating deposition of data into this database whilst ensuring proportionate controls on access will help create a robust and reliable database that serves the needs of NHS patients.

Systematically collecting evidence of the scientific and clinical validity of genetic variants is vital to provide an optimal service, and will also help to clarify the benefits and risks associated with actively searching for clinically actionable genes ('opportunistic screening').

A recurring theme concerned the volume of findings that might be generated, particularly VUS. Disclosing findings without understanding their significance could cause distress to patients and families, and delivering that information could strain limited resources. Consistent approaches to generating, interpreting and disclosing these findings will help. Ensuring that new knowledge is available to inform interpretation and, where appropriate and with consent, shared beyond the NHS, will help to make these systems more robust.

Recognising the patients' autonomous choices through enhancing current processes for seeking consent will help mitigate these potential harms. The report sets out the areas which should be explicitly addressed with patients in the consent process, including a thorough discussion of the impact, benefits, risks and uncertainties that arise. The nature of the test; the generation, interpretation and disclosure of IFs and VUS, the sharing of data and the potential for reanalysis and recontact are elements that should be explicitly addressed. Reanalysis of data and unsolicited recontact raise novel ELSI challenges and will require systematic policy development.

As with any new technology, ensuring equitable access is a key aspect of responsible implementation. Consistent approaches to patient referrals through gene lists and systematic approaches to reanalysis and recontact need to be developed. These must be supported by education for health professionals and patients, underpinned by robust mechanisms for evaluation and commissioning.

These measures will help ensure the responsible and ethical implementation of these technologies, optimising their utility for patients and families, minimising the potential harms and building public trust.

The report is available at www.phgfoundation.org/project/realising-genomics

Clinical genome analysis: setting standards, delivering diagnoses

Leila Luheshi, PHG Foundation



Many BSGM members will know that of the PHG Foundation's long-standing interest in the clinical applications of genome sequencing; our 2011 report *Next steps in the sequence* (<http://www.phgfoundation.org/reports/10364/>) was the first comprehensive examination of the potential clinical impact of the rapidly-developing next generation sequencing (NGS) field.

Since then, the NHS operating environment has shifted significantly; with the establishment of Genomics England, we are now expecting 100,000 genomes to be sequenced by 2017, as a valuable new resource for cancer, inherited and infectious diseases. Realising personalised medicine by making genome sequencing and analysis part of everyday clinical practice within the next few years is a laudable new goal for NHS transformation. Efforts are underway to prepare for this 'genomics revolution' – not least the establishment of a dedicated genomics programme for workforce training.

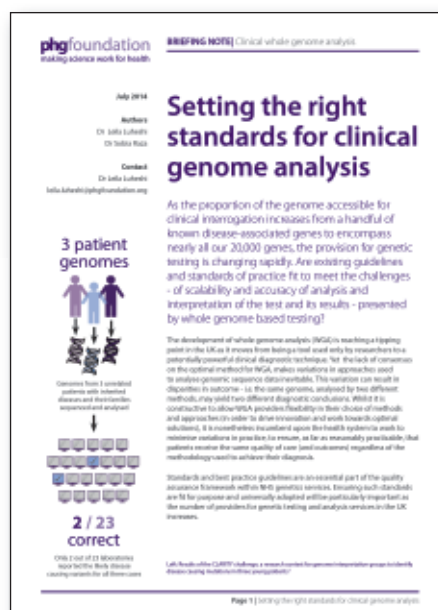
However, achieving accurate and clinically meaningful diagnoses through the use of

whole genome sequencing poses a range of challenges not necessarily understood outside the genetics community. Our Clinical Genome Analysis project (<http://www.phgfoundation.org/project/wgs/>) addresses this; guided by an expert steering-group, we have created a range of resources, which are outlined below, setting out the issues and making practical recommendations. Whilst little of their content will be revelatory to genetics professionals, they are a valuable means of communicating with other health professionals, commissioners and policy-makers.



Delivering the right diagnosis examines the critical steps in whole genome analysis, from raw DNA sequence to clinically actionable diagnostic report, highlighting the potential for variation and error between different pipelines and the need for standardisation to ensure that reporting is sufficiently reliable and accurate for routine NHS use. Key steps

include: establishing standards and best practice protocols for sequence generation, analysis and reporting; improving data-sharing and evidence base quality; and building necessary infrastructure.



Defining the role of a bioinformatician explains just what it is that bioinformaticians actually do and why it is so vital in genomic medicine. Roles include development and maintenance of algorithm-based analytical methods, databases, computational tools and workflows, as well as genomic data mining and interpretation. The briefing also sets out critical points of contact between bioinformaticians and other NHS professionals, and poses questions for policy-makers and health service providers seeking bioinformatics expertise.

Setting the right standards looks in greater detail at the increasing need for

Service Development

Segmental Overgrowth Syndromes NGS Service

Claire Langley and Emma Howard, Manchester Centre for Genomic Medicine.

standardisation of approaches to clinical genome analysis as demand grows. This is essential for delivery of consistent and quality-assured patient care, especially if the number of service providers increases as expected. The briefing also considers how to balance these quality requirements with the need to maintain service accessibility and innovation.

Sharing clinical genomic data for better diagnosis emphasises the urgent need for better data sharing across NHS institutions. Barriers include disincentives, costs, regulatory concerns and the absence of sustainable technical solutions for depositing and accessing genomic and clinical data. The serious opportunity costs of failure to act promptly are set against proposals for a way forward. These include mandatory data-sharing via a new, dedicated NHS data repository that is simple to use, meets the needs of clinicians and can interact with 100,000 Genomes Project infrastructure, as well as incorporating appropriate consent and confidentiality measures.

Resources from the Clinical Genome Analysis project are available to download free from
www.phgfoundation.org/project/wgs

The Manchester Centre for Genomic Medicine is pleased to announce the launch of a next generation sequencing (NGS) service for segmental overgrowth syndromes.

Segmental overgrowth syndromes are a heterogeneous group of rare diseases characterised by substantial localised or asymmetrical excessive tissue growth that can manifest both at birth and later in life. The umbrella term of 'Segmental overgrowth syndromes' encompasses disorders such as Megalencephaly-Capillary Malformation (MCM/MCAP) syndrome, Megalencephaly-Polymicrogyria-Polydactyly-Hydrocephalus (MPPH) syndrome, Congenital Lipomatous Overgrowth Vascular Malformations, Epidermal Nevi and Skeletal abnormalities (CLOVES syndrome), Proteus syndrome and Cowden syndrome.

Many segmental overgrowth syndromes have been attributed to mutations in genes of the phosphoinositide 3-kinase PI3K-Akt signalling pathway, with both germline and post-zygotic mutations associated. Key genes in this pathway are included in the Segmental Overgrowth Syndromes NGS panel, which features whole gene screening of *PIK3CA* and *PTEN*, as well as targeted screening of hotspot exons in *PIK3R2*, *AKT1*, *AKT3*, *mTOR* and *CCND2*. This test is capable of detecting post-zygotic mutations down to a level of 5%.

This panel uses long range-PCR as the target enrichment method and Illumina's MiSeq system to perform the next generation sequencing. Full bioinformatic analysis is undertaken and any potentially pathogenic mutations are confirmed using Sanger sequencing or ARMs-PCR. A

clear and informative report is issued within 40 working days.

Peripheral blood, saliva/buccal and fresh tissue samples are accepted for testing, with the latter being the preferred sample type.

For more information on the Segmental Overgrowth Syndrome NSG service please contact the laboratory:

Genomic Diagnostics Laboratory
Manchester Centre for Genomic Medicine
St Mary's Hospital
Hathersage Road
Manchester
M13 9WL
Tel: 0161 276 6122

New guidelines for the investigation of intellectual disability (ID)/ developmental delay (DD) in East Anglia

Louise Cameron, PHG Foundation and Alasdair Parker, Cambridge University Hospitals Trust

Finding a diagnosis is important for families and children affected by intellectual disability (ID) and developmental delay (DD); it may help to inform prognosis and care, and in planning future pregnancies. However, the journey to diagnosis can be a lengthy and anxious period for parents. In 2013 an online questionnaire completed by 25 consultant community paediatricians in the East Anglian region revealed variability in approach to diagnosis, and some divergence from the 2006 East Anglian diagnostic guidelines, in part reflecting the increased use of new genomic technologies in diagnosis such as array CGH.

This year, an updated version of the guidelines has been produced by the guidelines group, which includes clinicians, parents and clinical scientists, and was led by Dr Alasdair Parker, Consultant Paediatric Neurologist, Cambridge University Hospitals Trust. The guidelines describe the diagnostic investigation of children with moderate to severe ID/DD, and comprise a parents' guide, a clinician's guide, in the form of a diagnostic flowchart, and an evidence document to support the former two. The principle aims of the guides are to: describe best practice in diagnosis, incorporating the latest diagnostic technologies, and to improve the experience of parents and children in the diagnostic pathway.

The guidelines group drew on the experiences and expertise of the multidisciplinary group, to produce guides which take account not only of test yield, but also factors such as the severity and potential treatment for the condition, the impact of testing on the child and family, and logistics of sample collection. The

evidence document presents the evidence from the literature and regional laboratory experience.

Aetiology of ID/DD

The causes of ID/DD are known to include biological, environmental and genetic factors, with many cases being multifactorial. Genetic factors are identified or presumed as the cause of ID/DD in the greatest proportion of cases, with a spectrum of genetic abnormalities identified. Currently around half of cases are described as idiopathic, but new genomic technologies are impacting on this and reports in the literature describe increments in diagnosis rates in patients with idiopathic ID.¹

Genetics and genomics in ID/DD diagnosis

In line with national policy, the guide recommends array CGH as a first line test for this group of patients and is accompanied with a description of the capability of the test and the issue of variants of unknown significance (VUS). Potential reasons for referral to the clinical genetics service are described in second line testing, along with a discussion of testing for X-linked ID, including Fragile X.

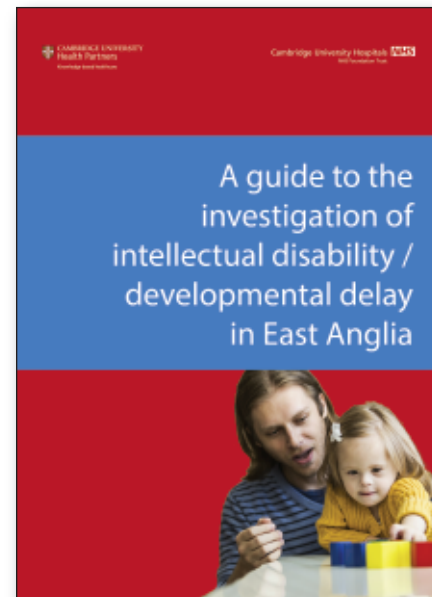
Initiatives such as the Deciphering Developmental Disorders (DDD) project and Genomics England's rare disease component are driving forward the application of whole genome and whole exome sequencing in this area. Whilst still in the research domain, these initiatives are described in the evidence document, which recommends dialogue between paediatricians and clinical genetics colleagues to capitalise on the diagnostic power of next generation sequencing in idiopathic ID/DD. The guide is scheduled to be updated in 2017, by which point the

diagnostic landscape is expected to have undergone further evolution.

The guides are available to download for free from **www.phgfoundation.org**.

Reference

1. Baker K, Raymond FL, Bass N. Genetic investigation for adults with intellectual disability: opportunities and challenges. *Current opinion in neurology*. 2012;25(2):150-8.



New economic evaluation of using array CGH testing for learning disability

Gurdeep Sagoo, PHG Foundation

phgfoundation
making science work for health

An economic evaluation of genome-wide high-resolution microarray comparative genomic hybridisation (array CGH) undertaken by the PHG Foundation - an organisation focused on the translation of genomic technologies into improved healthcare services - in collaboration with Guy's and St Thomas' NHS Foundation Trust and the UK Genetic Testing Network (UKGTN), shows that moving array CGH to a first line test would result in significant efficiency savings to clinical genetics services.

Around 1.2 to 1.5 million people in England and Wales have a learning disability according to the British Institute of Learning Disabilities and Mencap. Compelling evidence exists of the diagnostic benefits of array CGH for clinical genetics services. However, the perceived cost and complexity of the test, along with lack of consensus of NHS service configuration across laboratories, is hindering moves to use array CGH for routine first-line testing for cases with idiopathic learning disability, despite UKGTN testing criteria and guidance from professional bodies.

In 2006, PHG Foundation published a report on *array CGH in the diagnosis of learning disability* and a sister publication, *Parents as Partners*. Both reports, available at www.phgfoundation.org/reports/4968/, were well received by the clinical genetics community within the UK. In the report we recommended that not only should array CGH be implemented as a second line test but that further work should be undertaken to evaluate how array CGH would work in a first-line test setting.

The latest report, *Array CGH testing for learning disability – when is it worth it?*, also published on our website (<http://www.phgfoundation.org/file/16397/>) and presented by lead author Dr Gurdeep Sagoo to the BSGM conference in September 2014, sets out a cost-effectiveness analysis of using array CGH as a first-line test for learning disability within a single NHS clinical genetics service.

Data was analysed from a cohort of 1,590 patients with undiagnosed learning disability and developmental delay. The evaluation calculated a statistically significant positive net monetary benefit of £272, estimating that significant efficiency savings could be made within clinical genetics services by moving all array CGH testing to first line, rather than as a second line test following a negative karyotype. A cost per positive diagnosis of first line testing was calculated to be £2,544.42 versus £4,819.44 for second line testing.

Further savings in terms of benefits to patients and their families, of making both more and earlier diagnoses, were not included in this initial analysis, but can be expected.

Given the advances in DNA sequencing technology, economic evaluations are needed to provide timely evidence in order to support appropriate uptake of such advances into NHS clinical pathways. You can read more about this work and its results in the short report *Array CGH testing for learning disability – when is it worth it?*

(www.phgfoundation.org/briefing_notes/353/)

New Year Honours 2015 – Val Davison MBE

The BSGM is delighted to congratulate Val Davison, Scientific Advisor to the National School of Healthcare Science, who was awarded an MBE for services to genomic technologies in the New Year Honours list.

DERMATOGENETICS – a new special interest group linking the BSGM with dermatologists



Striking cutaneous phenotypes represent a fascinating aspect of clinical genetics, giving clues to multiple syndromic diagnoses and valuable opportunity for gaining insight into genetic mechanisms. At this year's BSGM annual meeting, the inaugural meeting of the *Dermatogenetics* group followed this theme. Professor Celia Moss highlighted the range of patterns that cutaneous mosaicism can present in the skin in her lecture *Back to Blaschko*. Our keynote speaker within the main conference, Professor John McGrath, gave his illuminating perspective on genodermatoses and the role of exome sequencing in the diagnosis and clinical management of these patients. Talks by junior clinical academics Sara Brown and Neil Rajan provided an overview of 'dermatology for geneticists' and 'genetics for dermatologists'.

Perhaps there is no better time to rekindle the interest in cutaneous phenotyping. Next generation sequencing technology offers the promise of identifying genes and genetic mechanisms responsible for many of the dermatological syndromes and signs which remain incompletely understood. The highly ambitious 100,000 Genome Project, which sets the UK apart as a world leader at population level sequencing, will represent a uniquely powerful resource for the research community, including rare disease research in dermatology.

Dermatogenetics aims to develop links between **genetic practitioners** with an interest in dermatology **and dermatologists** with an interest in genetics at this critical time. We aim to facilitate the sharing of knowledge and exchange of ideas in both clinical medicine and research.

Dermatogenetics, as a special interest group of the BSGM, aims to help by providing clinically relevant and up-to-date information for clinical dermatologists as well as those with an academic interest.

Specifically, *Dermatogenetics* aims to:

- Improve the recognition and phenotyping of cutaneous manifestations of genetic disorders, by closer working between dermatologists and geneticists.
- Provide a forum at the annual BSGM to discuss cases that have cutaneous manifestations at a multidisciplinary meeting involving dermatologists, geneticists and scientists.
- Offer opportunities for the education of specialty trainees in genetics and dermatology via seminars held at the annual BSGM and/or British Association of Dermatologists (BAD) meeting.

Upcoming meetings

Our next meeting is a half-day event that will be held at the BSGM annual meeting in 2015.

How to become a member of Dermatogenetics?

Membership is open to all individuals with an interest in the clinical and basic science of the hereditary aspects of skin disease. Expressions of interest should be directed to Sara Brown or Neil Rajan (contact details below). *Dermatogenetics* membership fees of £30 will be administered via the BSGM in line with other special interest groups.

Contact us:

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Gene therapy update

Andrew G. L. Douglas, Wessex Clinical Genetics Service

The European Society for Gene and Cell Therapy (ESGCT) hosted its 22nd annual congress this past October in The Hague, The Netherlands. Earlier in the year the same venue, the World Forum, had played host to Barack Obama and colleagues who met there for the Nuclear Security Summit. Whilst perhaps more modest in its public and media profile, the annual ESGCT conference is nonetheless also of global significance, at least to the medical world, and provides an excellent platform and meeting place for researchers and clinicians with an interest in novel gene and cell therapies.

The meeting always starts with an education and patient day, suitable for students, interested patients, clinicians and others looking for an overview of the subject. On this occasion an excellent introductory talk by Len Seymour, University of Oxford, covered the history of gene therapy from the first human trial for severe combined immunodeficiency caused by adenosine deaminase deficiency (SCID-ADA) immunodeficiency treatment in 1990 right through to the present day. As with the development of any field, there have been setbacks along the way, such as the death in 1999 of 18-year old Jesse Gelsinger who was enrolled in a gene therapy trial for ornithine transcarbamylase deficiency. However, the field has nevertheless persevered and continued to progress and today we stand at a point where a number of genetic disorders, including SCID-ADA, X-linked severe combined immunodeficiency (SCID-X1), beta-thalassaemia and adrenoleukodystrophy, have all been shown to be treatable by gene therapy.

A growing number of gene therapy clinical trials are currently in progress. In

Milan, 14 patients with metachromatic leukodystrophy have been transplanted with autologous haematopoietic stem cells (HSCs) that were transduced with a lentiviral vector carrying a working copy of the *ARSA* gene. High-level stable engraftment has been achieved with corresponding arrest of the neurodegenerative condition. In London, a team led by Bobby Gaspar and Adrian Thrasher at University College London have used a similar approach (using a gammaretroviral vector containing an optimised *ADA* gene) to treat patients with SCID-ADA. Wiskott-Aldrich syndrome is also being treated in a similar way. The use of genetically corrected autologous HSCs instead of an allogeneic donor transplant enables a less severe myeloablative regimen to be used and avoids the subsequent problems of immunosuppression. The risk of graft-versus-host disease is also avoided. Plans exist to clinically trial HSC gene therapy approaches in patients with Hurler and Krabbe disease.

Two diseases that have been in the gene therapy pipeline for some time are cystic fibrosis (CF) and Duchenne muscular dystrophy (DMD). The UK CF Gene Therapy Consortium has recently completed data collection on a multi-dose clinical trial of monthly, nebulised, liposome-based *CFTR* replacement. The results of this trial are eagerly awaited. DMD gene replacement therapy, which employs a shortened form of dystrophin known as microdystrophin, remains for now at the preclinical stage, albeit with impressive results in animal models. On the other hand, RNA-based therapies for DMD have been in clinical trials for some years now. The stop codon read-through drug Ataluren (now known as Translarna) has been conditionally licensed by the

European Medicines Agency since August 2014 and its producer, PTC Therapeutics, is seeking to recruit patients to a confirmatory phase III trial. In addition, trials of two exon-skipping oligonucleotide drugs (Eteplirsen, Sarepta Therapeutics; Drisapersen, Prosensa) have been taken to phase II trials. After initial concerns about a lack of clinical efficacy in the case of Drisapersen's results in 2013, a better understanding of DMD's natural history together with more appropriate patient group stratification has led to renewed optimism that clinical benefit will be achieved with this drug. In comparison, Eteplirsen-treated boys continue to show a sustained maintenance of ambulatory ability over a two to three year period as compared to the expected natural history course of the disease.

New technologies are helping to extend the reach of gene therapy research. The development of chimeric antigen receptors (CARs), which are genetically encoded designer antibody-like molecules expressed by T-cells, allows the targeted destruction of tumours expressing specific antigens, with accompanied T-cell clonal proliferation targeting the same tumour antigen. Up to now this approach has been pioneered mainly in the treatment of refractory leukaemias. However, its application to the potential treatment of other tumours is clear. It has been said that gene therapy is only likely to become mainstream if it can tackle common diseases. Treatment of cancer would certainly fit this bill. However, it may also be possible to treat conditions such as diabetes by use of genetically engineered metabolic sensor-effector implants. A synthetic biology approach could allow design of a genetic circuit whereby a

NIHR Collaborative Group for Genetics in Healthcare – update

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

glucose sensor expressed by a cellular implant could be linked to insulin secretion.

The next ESGCT congress will be in Helsinki from 17-20 September 2015. For those interested in the UK gene therapy scene, the British Society for Gene and Cell Therapy (BSGCT) has its 2015 conference in Glasgow from 9-11 June 2015. Both societies are very keen to establish links with other societies and groups and BSGM members may wish to consider what collaborative possibilities may exist.

As a clinical geneticist, I think we ought to be aware of current gene therapy trials, at the very least so as to be able to inform our patients about them. For those who are interested, there is also the opportunity to get involved. European funding for such research is currently strong, with initiatives such as Horizon 2020 and the Innovative Medicines Initiative (IMI) setting aside substantial funding pots for research into novel therapies. Indeed, there has never been a better opportunity to develop gene therapies for rare genetic diseases. Gene therapy is not just a story about something that may or may not happen some day in the future. It will happen and in fact it is happening now. As a specialty, I believe we have a chance to play a central role in the development of this field as it takes its first steps towards becoming a mature discipline.

1. Practical Research in Genetic Healthcare Session: BSGM Liverpool 2014

At the **National Institute for Health Research (NIHR) Clinical Research Network (CRN)** session at the annual conference of the BSGM in September 2014, researchers gave updates on their ongoing studies and appealed for help recruiting to new studies.

Chair **Dr Shane McKee** kicked off the session by highlighting the importance of genetics centres helping one another and sharing work, saying it was *"pivotal in pulling patients together and coordinating research."*

Dr Serena Nik-Zainal was the first to speak, telling the audience about her study into mutational signatures in cancer. (UKCRN 15956: <http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=15956>) She described the way that her team have been working to find out how the thousands of mutations present in a cancer genome

arose and matching these to exposure to chemicals such as those through smoking, exposure to UV and recurrent infections.

She detailed the mutational processes they have already found that *"leave a characteristic mark - a signature - in the genome"* causing normal cells to turn into cancer cells.

The website for the INSIGNIA study is now up and running (<http://www.mutationsignatures.org/insignia>), with sections for patients and clinicians who are involved. They are still looking for participants with DNA repair disorders to take part.

Next, **Dr Kemi Lokulo-Sodiye** spoke about the launch of the STAARS study investigating Russell Silver syndrome (RSS). This rare childhood-onset disease leaves adults with a shorter than average stature. Dr Lokulo-Sodiye said that parents are often concerned about whether their children should be treated



Speakers & Chairs: L to R Shane McKee, Gillian Crawford, Kemi Lokulo-Sodiye, Diana Baralle, Serena Nik-Zainal, Lyn Chitty, John Burn & Oliver Quarrell

“One of the biggest issues in genetic testing at the moment is whether to report back incidental findings”



A picture says 1000 words: GenRes members Louise Nevitt, Miranda Squires & Karen Tricker

with growth hormone, because it is unknown whether this has an effect on final height. By interviewing those with RSS, and taking a medical history, they hope to be able to provide a definitive answer.

"We hope this study will provide more information about whether the treatment affects patients' final height, so we can better advise these families. This will also help us provide guidance for healthcare professionals who work with those affected by Russell Silver syndrome."

They also hope to be able to find the reason why children with RSS have problems with eating and are often underweight, but adults are more likely to be obese. This study is described in more detail on page 12.

Next to speak was **Dr Oliver Quarrell**, consultant clinical geneticist at Sheffield Children's Hospital. His study into juvenile Huntington's disease (JHD) will assess which healthcare services are being used by people with JHD and their carers.

Dr Quarrell will also weigh up the potential benefits of more 'modern' services such as virtual appointments, which he believes may be useful for JHD patients who may find it difficult to travel.

By having a better understanding of how Huntington's disease develops in those under 20 compared to the adult-onset disease, he hopes that doctors will be able to better monitor patients, and *"we will be able to better judge the effect of therapies and treatments"*, said Dr Quarrell. This study is described in more detail on page 13.

One of the biggest issues in genetic testing at the moment is whether or not to report back incidental findings (IFs). **Gillian Crawford** is currently investigating healthcare professionals' experiences of discussing IFs with patients.

Her team, based at the University of Southampton, have already found that it is challenging for health professionals to bring up this topic. Part of the problem is that there isn't a standard approach to

the issue of incidental findings among genetics services. Having to discuss potential incidental findings alongside talking about genetic testing can be *"overwhelming"*.

However, patients were overall *"very positive"* about receiving incidental findings, giving an example of a family who were offered regular screening after their child was found to be at higher risk of Lynch syndrome. This study is described in more detail on page 13.

Professor Lyn Chitty gave an overview of the RAPID study (UKCRN 5774: <http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=5774>). She described the project's work on non-invasive prenatal testing (NIPT) for common trisomies. NIPT has reduced the need for invasive testing by 80 percent so far, and the team are now working towards giving a *"definitive diagnosis for a wider range of conditions"*.



GenRes & Speakers

“This NIHR CRN session was also attended by over 20 GenRes genetics research nurses, counsellors & coordinators who recruit to UK CRN genetics portfolio studies”

Patients and healthcare professionals are “universally positive” about NIPT: they value the safety and appreciate earlier diagnosis, she added.

Professor Chitty thanked audience members for their contributions to the study's sample bank, saying it was “absolutely critical” to the success of the research. By the end of 2014, non-invasive testing should be available in more than 60 countries.

She also spoke about the EACH study, which is now being prepared for publication (UKCRN 11729: <http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=11729>). The technique, using array CGH for detecting fetal chromosomal abnormalities, meant an extra eight percent of chromosomal abnormalities were found over using NIPT alone. “The majority of chromosomal abnormalities would be missed if we didn't have a whole-genome approach,” said Professor Chitty.

The session was rounded off by **Professor John Burn**, who announced that the CAPP3 study was seeing its first patients, and that the definitive 10-year follow-up study for CAPP2 is due next year.

He described how the NIHR Clinical Research Network is crucial to such research trials, both in terms of helping to recruit patients and developing registries. Despite the effort involved in setting up clinical trials, he said, it was worthwhile to keep going because of the huge potential benefits for patients.

Professor Burn reminded the audience of the research that has allowed some genetic disorders to become treatable, most notably phenylketonuria and familial adenomatous polyposis.

“Even though it's a long process, the families gain immensely from being a part of research, and I think we should be very enthusiastic about looking for trials that our patients could take part in,” he said.

This NIHR CRN session was also attended by over 20 GenRes genetics research nurses, counsellors and coordinators who recruit to UK CRN genetics portfolio studies (<http://www.bsgm.org.uk/genetics-healthcare-research/genres/>). This was an opportunity for the GenRes personnel to hear about the outputs of the research studies where they were involved in the recruitment process and network with Genetics personnel from across the UK.

2. The Russell-Silver STAARS study begins in UK

Recruitment for the Study of Adults and Adolescents with Russell-Silver syndrome in the UK (STAARS UK), UKCRN 16623, is now underway.

Russell-Silver syndrome (RSS) causes poor in-utero growth, short stature, feeding difficulties with a marked lack of subcutaneous fat and frequently a broad forehead. The researchers want to know more about the rare condition, and find out whether growth hormone treatment is beneficial to increase the height of those affected.

“It is a rare disease and there is a lot more to learn. From patients and working with the Child Growth Foundation, we know that patients and their families want more information”, said Dr Kemi Lokulo-Sodipe from the University of Southampton, speaking at the annual conference of the British Society of Genetic Medicine.

Children with RSS often have problems with eating, as they may have an aversion to food, a cleft palate, lack of appetite, and/or gastrointestinal reflux. But adults generally have fewer issues and, conversely, may become overweight in later life. Part of the research will involve investigating why this is the case, and interviewing the patients to ask if and when eating habits and preferences changed.

Children who are small at birth and do not ‘catch-up’ in their growth at four years old can be given growth hormone treatment, which involves daily injections for up to ten years. As stated by Dr Lokulo-Sodipe, *“for parents of children affected with Russell-Silver Syndrome, it can be hard to decide whether or not to treat their children with growth hormone. We hope this study will provide more information about whether the treatment affects patients' final height, so we can better advise families. This will also help us provide guidance for healthcare professionals treating patients with RSS.”*

In 60-70% of RSS cases an underlying epigenetic cause is found. In 50-60% the cause is hypomethylation at the imprinting control region at chromosome 11p15. In 5-10% maternal uniparental disomy of chromosome 7 is found.

The researchers aim to recruit 100 patients with RSS who are aged 13 years and above. A single study appointment involves a review of their medical history, examination, blood and genetic tests, height, weight and body composition measurements. Approximately one third of the participants will be invited for an in-depth interview about their experience of living with RSS. *“We plan to speak to patients with RSS to find out how their*

“The families for whom incidental findings were found were keen to receive this information”

condition affects them and how it's changed throughout their lifetime," said Kemi Lokulo-Sodiye.

For more information please email: STAARS@uhs.nhs.uk.

Further information about this study, Study of Adults and Adolescents with Russell Silver syndrome in the UK is available at: <http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=16623>

3. Health professionals need support in managing incidental findings

As technology for genetic testing improves, the chance of finding unexpected results increases. Discussing Incidental Findings (IFs) with patients and their families is a growing concern for clinicians, a study has found.

Gillian Crawford and her team at the University of Southampton (www.cels.soton.ac.uk) spoke to 16 family members and 32 healthcare professionals (HCPs) across the UK about their views and experiences about incidental findings from genetic tests. While families were mostly keen to hear about these results, healthcare professionals found their clinical management challenging, the research found.

The study also found that practice varies considerably and that many HCPs do not routinely tell patients about the possibility of incidental findings before testing takes place, and thus do not take specific consent for reporting these findings.

"Centres around the country have their own forms and their own care pathways, and there was no standard approach to the issue of incidental findings," said Ms

Crawford. "We found a lot of variation: some talked about it in reasonable detail, some mentioned it very superficially, and some didn't mention it at all."

Ms Crawford suggested that the sheer amount of information that HCPs could give to patients and their relatives is overwhelming. Whilst technologies are still changing rapidly and debates about what incidental findings are looked for continue, it can be difficult for HCPs to know what they should communicate. Also, once an incidental finding is found, the interpretation of its significance may depend on other factors, for example, information about the family history, and HCPs found this situation tricky, particularly if they considered this information would be 'out of the blue' for patients and their families.

However, the families for whom incidental findings were found were keen to receive this information, the study reported. "The families talked very positively about having received this information: it was helpful and they could access interventions," said Ms Crawford. "Even if treatments weren't currently available, they hoped they would be in the future. They found it empowering to have the information."

Ms Crawford spoke about a patient whose genetic testing revealed that he had a Lynch syndrome mutation. His father described the finding as a "lucky break" because it meant his son could receive regular screening.

Around one percent of array CGH tests will return an incidental finding, but this figure could be much larger for, exome and whole genome sequencing.

The second stage of the study is due to start soon, around 300 healthcare

professionals will be asked to detail their views on the consent to and disclosure of incidental findings in a questionnaire. "This part of the study will focus more on who takes consent, what they think this process should include, how broad or specific the discussion should be, and what choices should be given to patients about how much is disclosed," said Ms Crawford.

This UKCRN portfolio study 10917, Incidental Findings (IFs) from genetic tests is funded by a NIHR Clinical Doctoral Research Fellowship to Gillian Crawford

<http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=10917>

4. Patients needed for Juvenile Huntington's disease study

Researchers at Sheffield Children's Hospital are recruiting patients for a study into juvenile Huntington's disease.

Dr Oliver Quarrell, consultant clinical geneticist, and his team want to see which healthcare services are being used by people with JHD and their carers.

People with Huntington's disease develop severe problems with movement and behavioural problems that worsen as the disease progresses. It is a life-limiting condition that typically begins in adulthood. Those who develop symptoms before the age of 20 are said to have Juvenile Huntington's disease (JHD).

"It is recommended that people with Huntington's disease should be cared for by a multi-disciplinary team, but there isn't a lot of evidence for this," said Dr Quarrell. "We want to know how best to care for people with this condition."

“The researchers say there is a lot about Juvenile Huntington’s disease which is not yet understood”

Dr Quarrell and his team will investigate whether a 'one-stop' clinic would be beneficial to JHD patients and their carers. He also suggests that 'virtual clinics' could be of use to the patients, as it will mean they will not have to travel – something that can be a problem for those with a movement-limiting disease.

Specialist clinics are available for people with adult-onset Huntington's disease, who may need the help of speech therapists and physiotherapists. But these may not always be suitable for those with JHD as they may require different expertise, such as paediatric neurologists or child psychologists.

The team also hope to develop a rating scale to provide a better assessment of disease progression in people with JHD. *"Having a better way to monitor the patients' condition will mean we will be able to judge the effect of therapies and treatments,"* said Dr Quarrell.

The researchers say there is a lot about JHD which is not yet understood, such as whether juvenile onset leads to a shorter life expectancy, or a faster disease

progression rate. *"As well as collecting patients together for this study and finding out the best way of organising services, I hope we can use it to address the other questions which are unclear,"* said Dr Quarrell.

"This is a tremendous opportunity to gather all the cases of JHD in the country together, but to do that we need the support of the clinical genetics community," he added.

The team are asking clinicians to check genetic databases to find patients with more than 50 CAG repeats in the Huntington's gene and identify those who had an onset less than 20 years. They are hoping to interview 12 families and send questionnaires to the others. 30 responses to the questionnaires are required. The team will also interview up to 40 health care professionals who currently look after patients/families with JHD.

Further information about this study UKCRN 17578, Services for Juvenile Huntington's Disease is available at: <http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=17578>

Further information on portfolio studies can be found on the UK Clinical Research Network (UKCRN) Portfolio Database <http://public.ukcrn.org.uk/search/>. If you think your research could benefit from the NIHR Clinical Research Network: Genetics services visit

http://www.crn.nihr.ac.uk/about_us/genetics/

or email Dr Gill Borthwick, the Genetics National Research Coordinator, on Gillian.borthwick@ncl.ac.uk. These articles were prepared by the Progress Educational Trust on behalf of the Collaborative Group for Genetics in Healthcare (CGGH), working with the NIHR Clinical Research Network: Genetics. For further information on the Collaborative Group for Genetics in Healthcare (CGGH) visit <http://www.bsgm.org.uk/genetics-healthcare-research/>

Glasgow University MSc Medical Genetics Teaching Team win UK Prospects Postgraduate Award

The MSc Medical Genetics at the University of Glasgow has recently won the title of Best Teaching Team (Science, Engineering and Technology) in the UK-wide 2014 Prospects Postgraduate Awards. The award was collected by BSGM member, Professor Edward Tobias (Honorary Consultant in Medical Genetics and Clinical Director of the course), and by Dr Maria Jackson (Senior University Teacher and course Programme Director). The glittering awards ceremony, on 10 November 2014, at The Midland Hotel in Manchester, was attended by more than 150 leaders in postgraduate education provision.

Nominations for these prestigious teaching awards were made by students, and the entries were judged by a ten-member panel that included representatives from the National Union of Students, the UK Council for Graduate Education, the Higher Education Academy and the Higher Education Funding Council for England.

David Walker, a student who is to graduate with his MSc in Medical Genetics in December 2014 said: *"I am so pleased for the Medical Genetics team to be recognised for their excellence – not just internally, at the University, but across the country. The team bring a unique personal touch to the course and complement each other's strengths, providing one of the most enjoyable experiences I've had during my five years at the University."*



The Prospects Postgraduate Awards, sponsored by University Business, are annual accolades solely dedicated to celebrating best practice in teaching and the most exciting developments in UK postgraduate education. Prospects, the UK's leading postgraduate education publisher, maintains the official postgraduate course database. The Prospects Chief Executive said: *"It's fantastic to see such a high calibre of entries from the UK's leaders in postgraduate education. Each year we're overwhelmed by the support and excitement we receive. Congratulations to the Medical Genetics team who have demonstrated a wide breadth of ways to support their students."*

Professor Tobias is lead author of undergraduate and postgraduate textbooks on medical genetics and is Chief Investigator of a Wellcome Trust funded research project involving exomic sequencing for rare disorders. He has won four personal teaching awards since 2012, including three Student Representative Council awards from students themselves. In addition, the Glasgow MSc Medical Genetics teaching team have together won two other university awards for teaching excellence in 2014. The internationally popular MSc programme includes course options on Genomics and on Cancer Sciences and it receives much invaluable input from NHS clinicians and clinical scientists.

Peer support for people with a family history of breast cancer

Nik Thoren, Breast Cancer Care

Breast Cancer Care's unique *Someone Like Me* service has further expanded the support it offers.

The service, which provides support over the phone from trained volunteers for people affected by breast cancer, now offers the opportunity for people who have a faulty BRCA gene to speak to someone with a similar experience. This will give anyone worried about their situation the chance to talk openly with someone who understands how they may be feeling.

Since it was founded more than 40 years ago, peer support has been central part of Breast Cancer Care's work. This latest development is the result of an increase in the number clients wishing to speak to someone about their experience of genetic testing and making decisions about risk-reducing treatments.

Jackie Harris, Clinical Nurse Specialist for Family History and Breast Health at Breast Cancer Care, said: *"We are really happy to now offer tailored support to those facing difficult decisions about family history through Someone Like Me. We work alongside a number of genetic counsellors and geneticists around the country when developing our healthcare professional training, patient information and patient services. We look forward to working more closely with genetic counsellors and are so grateful to our amazing volunteers providing this vital emotional support."*

Jo is one of the new *Someone Like Me* volunteers. She said: *"I was told I had the BRCA1 altered gene nine years ago at the age of 30. My sister was given the all clear from the genetic testing, which left me feeling like it was a road that I would*

have to walk alone. I was fortunate to be well supported by my genetics team, but through the years I've met other women in a similar position and realised not everyone has that support. I am passionate about supporting other women through the Someone Like Me service, to help ensure no one feels they're alone when faced with big decisions about their future."

To access the *Someone Like Me* service, people can call 0345 077 1893, email someonelikeme@breastcancercare.org.uk or text SLM and their name to 07889 001289.

For further information about the service visit www.breastcancercare.org.uk/someonelikeme

Psychiatric Genetics for Genetic Counsellors

In February, the Translational Genetics Group at Bournemouth University is running a two day intensive workshop titled: *Psychiatric Genetics for Genetic Counsellors*. Research carried out in Canada by Dr Jehannine Austin's group at the University of British Columbia has shown that people with psychiatric conditions and their families are interested in receiving genetic counselling. However, research has also demonstrated that there are barriers obstructing clinicians from providing genetic counselling services for this population.

In this two-day workshop, a group of 20 learners will receive intensive, practically-oriented instruction and support designed to increase confidence and competence with providing effective genetic counselling services for people with psychiatric disorders and their families. Topics include: orientation to psychiatric diagnoses, in depth review of the genetics of psychiatric disorders, the relationship between explanations for cause of illness and stigma, psychosocial issues that attend changing patients' explanations for cause of illness and strategies for managing them.

Funded by Bournemouth University's *Fusion Investment Fund* and facilitated by Kevin McGhee PhD and Jehannine Austin PhD CGC/CCGC, this workshop will also serve as a platform to establish a network of individuals who can lead the consolidation of the emerging area of psychiatric genetic counselling as a specialist genetic counselling practice area within the UK.

Demand is high; already we have had registrations from the UK, Israel, USA, Norway, Germany and Romania. Members of the BSGM interested in further information on the field of psychiatric genetics are encouraged to email kmcghee@bournemouth.ac.uk for further details.

Noticeboard

ESHG 2015



June 6-9, 2015

At the SECC in Glasgow in conjunction with the British Society for Genetic Medicine.

Conference report

European Society of Human Genetics Milan, Italy. May 31 – June 3 2014

Harsh Sheth- PhD student, Institute of Genetic Medicine

I was awarded travel grant to attend the European Society of Human Genetics 2014 conference in Milan, Italy. The conference discussed latest trends, technologies and clinical applications in various areas of human genetics. My abstract titled *Polymorphism in genes CYP2C9 and ODC1 involved in aspirin handling influence colorectal cancer risk* was selected for poster presentation. The poster presented results of investigating the impact of 32 SNPs in 9 genes on colorectal cancer (CRC) risk using the Leeds Colorectal Cancer Panel, which contained 1910 cases and 1276 controls. The novel data indicated a significant inverse association between the minor alleles of 2 SNPs in the *ODC1* gene with CRC risk. Upon stratification by cancer site, minor allele of a SNP from *ODC1* and *CYP2C9* gene showed inverse association only with colon cancer suggesting site-specific influence. The

poster received attention from several noted peers and colleagues such as Professor Andrew Read while a group from University of Helsinki showed interest in collaborating to validate our epidemiological results. Apart from the talks presented by eminent scientists such as Professor Mario Capecchi and Professor Sir Michael Stratton, the conference conducted an interactive debate titled *What IF... (Incidental Findings)* where different approaches developed by the societies from both sides of the Atlantic for counselling patients for 'incidental findings' were debated. In the end, I would like to thank my supervisors Professor Sir John Burn and Dr. Mike Jackson for their unwavering support and guidance and to the British Society of Genetic Medicine for awarding me with the travel grant to attend the conference.

Annual General Meeting

This year, our Annual General Meeting will take place during ESHG 2015 in Glasgow.

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

If there are any matters which members wish to raise would they please send them to the General Secretary, Dr Adam Shaw, Clinical Genetics, 7th Floor Borough Wing, Guy's Hospital, Great Maze Pond London SE1 9RT by Monday 4 May 2015

email: adam.shaw@gstt.nhs.uk

Welcome to New Members

64 new members were accepted by the British Society for Genetic Medicine in June and September 2014.

Miss Nazya Azem	CGS
Dr David Brawand	BSGM
Miss Celia Brown	Lab Trainee
Dr Andy Buckton	ACGS
Dr Anne-Cecile Burgeire	Lab Trainee
Dr Ruth Carey-Heaton	AGNC
Miss Heather V Chalinor	AGNC
Miss Fiona Chamberlayne	AGNC
Dr Graeme Clark	BSGM
Miss Trudie Cottrell	Lab Trainees
Dr Anthony Dallosso	Lab Trainee
Dr Esther Dempsey	CGS
Dr Natalie A Forrester	Lab Trainee
Mr Pierre Foscett	ACGS
Miss Tamsin Gannon	CGS
Mrs Gael Ganz	AGNC
Dr Nicole Gassan	Lab Trainee
Dr Gabriella Gazdag	CGS
Mrs Louise Gillies	AGNC
Ms Joana T G A Gomes	AGNC
Mrs Jennifer Gorrie	AGNC
Mrs Elspeth M Graham	AGNC
Dr Mark J Hamilton	CGS
Mr Eoin Hanney	AGNC
Mrs Claire Hodgkiss	ACGS
Dr Caroline Hutchison	CGS
Miss Rachael E Irwin	Lab Trainee
Dr Shatha Janabi	CGS
Miss Sian Jenkins	AGNC
Dr Rachel Jones	CGS
Mr Garan H L Jones	ACGS
Ms Areeba Khan	AGNC
Ms Kelly Kohut	BSGM
Miss Emily Lamb	AGNC
Miss Frances Lane	AGNC
Dr Laura Lopez Pascua	Lab Trainees
Prof Irwin Maclean	BSGM
Mr Robert J Macleod	ACGS
Dr Rowena Mitchell	Lab Trainee
Dr Dylan Mordaunt	CGS
Prof Azim Nejatizadeh	ACGS
Miss Katie Nelson	AGNC

Mr Rodney Nyanhete	Lab Trainee
Dr James O'Byrne	CGS
Dr Alisdair Philip	AGNC
Miss Ellen M Quinn	AGNC
Ms Belinda Rahman	AGNC
Dr Sara Rey	Lab Trainee
Dr Ruth Richardson	CGS
Dr Elaine Robertson	ACGS
Miss Antoniya Ruseva	AGNC
Dr Gavin Ryan	Lab Trainees
Dr Gurdeep Sagoo	BSGM
Dr Schaida Schirwani	CGS
Miss Claire Shea-Stokes	AGNC
Prof Mohammed Shekari	ACGS
Dr Sivagamy Sithambaram	CGS
Prof Philip Stanieri	BSGM
Miss Anna Tanska	ACGS
Dr Janet Taylor	BSGM
Dr Mikel Valganon	ACGS
Mr Marc Wadsley	Lab Trainees
Miss Elizabeth Watson	Lab Trainees
Miss Sinead Whyte	AGNC

Direct Debit Subscriptions for 2015/2016

The membership subscriptions will be collected by direct debit during 5-7 April 2015 (see table below for breakdown for each constituent group)

Subscription	BSGM only	ACGS	AGNC	CGS	Genetic Laboratories Trainees	CGG only	DG only
BSGM component	55	40	40	40	40	40	40
Payable to Constituent Society	-	15	25	25	15	15	15
TOTAL	55	55	65	65	55	55	55
Cancer Genetics Group	-	15	15	15	15	-	15
Dermatogenetics Group	-	15	15	15	15	15	-
TOTAL including CGG membership	-	70	80	80	70	-	70
TOTAL including DG membership	-	70	80	80	70	70	-
TOTAL including CGG and DG membership	-	85	95	95	85	-	-

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

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

For those members who do not pay by direct debit the Society will be contacting you shortly. Membership Subscriptions are due on 1 April 2015, all payments to be received by the end of April 2015.

Affiliate Membership of the European Society of Human Genetics

For those members who have also opted to take out affiliate membership of the ESHG an additional fee of £44 will also be collected – please note that this rate has not changed as per 2014/2015 through negotiations.

Your ESHG membership will be renewed if subscribed through BSGM unless we are notified by yourselves otherwise before the end of March 2015.

Forthcoming conferences

(CGS) Clinical Genetics Society Spring Conference 2015: 03 March 2015

Venue: Royal College of Physicians,
11 St Andrews Place, London NW1 4LE
Contact: bshg@bshg.org.uk
Website:
<http://cgs2015.bshgconferences.org.uk/>

Dysmorphology Meeting: 04 March 2015

Venue: 33QS lecture theatre at the National
Hospital for Neurology and Neurosurgery, 33
Queen Square, London WC1N 3BG
Contact: bshg@bshg.org.uk
Website:
<http://cgs2015.bshgconferences.org.uk/>

(CGG/ IMPAHC) 14th International Meeting on the Psychosocial Aspects of Hereditary Cancer, in Conjunction with the UK Cancer Genetics Group Spring Meeting 2015: 05-07 May 2015

Venue: Manchester Conference Centre,
Sackville Street, Manchester M1 3BB, UK
Contact: bshg@bshg.org.uk
Website:
<http://cgg2015.bshgconferences.org.uk/>

(ESHG) European Human Genetics Conference: 06-09 June 2015

Venue: SECC, Glasgow, Scotland, United Kingdom
Contact: conference@eshg.org
Website:
<https://www.eshg.org/eshg2015.html>

(ASHG) American Society for Human Genetics Annual Meeting: 06-10 October 2015

Venue: Baltimore, Maryland, USA
Contact: ashgmeetings@ashg.org
Website: <http://www.ashg.org/2015meeting/>

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

BSGM News Editor



Deadline for contributions for next issue is 30 April 2015

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Editorial

As we go to press, Leicester geneticists spill the beans on Her Majesty the Queen's ancestry and posit the existence of a blue-eyed blonde Richard III. This could all be cleared up with a few royal exhumations, (which won't be happening any time soon!). Our Royals are not overly keen on genetic investigations (Richard III's skeleton being not the only one in the cupboard) although HRH The Duke of Edinburgh did supply a DNA sample for Jean-Jacques Cassiman's investigation of the 'Ekaterinburg' bones of Tsar Nicolas and his family, Prince Philip being related to the Tsarina Alexandra. Nevertheless the Leicester (and others) study shows the power of patrilineal and matrilineal investigations using Y chromosome and mitochondrial DNA studies respectively.

Also in the news, 23andMe have another go at launching their DNA screening test, after it was banned in the US. One of its sponsors is Google, and since the saliva test tubes have to be sent to the Netherlands before being tested in the US, one could be forgiven for asking which country will be the eventual recipient of any tax paid. 23andMe has now hired a dedicated team working on obtaining FDA approval.

And so to this bumper issue of the ACGS section news and many thanks to all those contributors who have slaved away over a hot sequencer or endured hours of conference presentations, to bring us some

excellent cutting-edge reports. First up are two articles with a common theme: sharing genetic (sequence change) information. Perhaps the most obvious question is why, after two or three decades, do we appear to be no closer to a common solution. Too many databases, people!

Next up is Ian Berry's excellent article/advertisement for Leeds' NGS service, which looks very impressive. Nice to see Primary Ciliary Dyskinesia feature in the mix; an active interest in a previous life.

Caroline Sarton then gives us a conference report on sudden cardiac death, followed by a brief review/advertisement of Oxford's Cardiac Arrhythmia Panel. It's very impressive that the lab has been able to apply this to tissue from paraffin blocks, thus enabling retrospective family studies to be carried out.

It's encouraging to receive an article from a Genetic Technologist, and we have one such in the form of a report by Emma Clark on the recent GT meeting.

Finally, Carolyn Tysoe and others from Exeter show the way towards a paperless office, describing their success in emailing genetic reports using StarLims. Further congratulations are due to them for sneaking the word 'postpeople' past the editors!

Martin Schwarz

Sharing genetic variant data across NHS labs – are we there yet?

Andrew Parrish, Melissa Sloman, Martina Owens and Sian Ellard
Exeter Genetics Laboratory

We thought we were getting close when Graham Taylor's vision of DMuDb, a database of mutations reported by diagnostic genetic laboratories, became reality through the National Genetics Reference Laboratory (NGRL Manchester) funding. Andrew Devereau's team worked hard to establish the infrastructure and support laboratories to upload their data. The result was 51,575 variant reports from 219 genes as of March 2014. But then the money ran out and the future looked glum. Fortunately DECIPHER has come to the rescue, an online database of genetic variation and associated phenotypic information in patients with rare disorders based around an interactive genome browser (<https://decipher.sanger.ac.uk>). Originally set up in 2004 to capture copy number variation, DECIPHER has been expanded to also include single nucleotide variants and small insertions/deletions.

The Exeter Genetics Laboratory provides genetic testing for >75 rare disorders so finding novel variants is a frequent occurrence. Databases like EVS (<http://evs.gs.washington.edu/EVS/>) and ExAC (<http://exac.broadinstitute.org/>) can be useful but even better is the knowledge that another diagnostic laboratory has identified patient(s) with the same variant. In 2012 and with the help of an excellent work experience student, Kelsey Loudon, we embarked on a project to upload all pathogenic/likely pathogenic and variants of uncertain clinical significance reported between 1996 and 2010 into DMuDb. Kelsey handed the baton to Sophie Robertson, Annabelle Whatmough, and Hannah Jones who assisted with the annotation of data stored within StarLIMS from 2010. We are very grateful to Jawahar Swaminathan who transferred our data from DMuDB and uploaded the additional variants from StarLIMS. In total we have

Developing a network for sharing genetic variant data across Australia & New Zealand: lessons from overseas?

Graham Taylor, Desiree du Sart & John-Paul Plazzer, Victorian Clinical Genetics Laboratories, Murdoch Childrens Research Institute, Victoria, Australia

now submitted 2970 variants from >50 genes to DECIPHER.

The genetic variants are stored within the DECIPHER NHS data-sharing project. This limits viewing rights to other NHS genetics laboratories who can see which lab has identified a variant of interest and contact them directly. Data are submitted in pseudonymised format with the internal laboratory number and laboratory as the identifiers. This is a first step towards global genomic data sharing (see the Global Alliance for Genomics in Health website <http://genomicsandhealth.org/>).

For the continued success of this project, it is important that the benefit gained from sharing data between laboratories is greater than the effort required to upload. With this in mind, we have set up an export from StarLIMS and use the Mutalyzer (<https://mutalyzer.nl>) bulk position converter tool to convert our variant positions to genomic coordinates to conform to the format required by the automated DECIPHER upload tool. We will run this on a monthly basis in order to keep up to date until our dream of live data export/upload to DECIPHER becomes a reality. If other labs are contemplating similar mutation uploads then we'd be pleased to share our experience as the full benefits will only be realised when sharing these data becomes routine practice. Why not get a head start now before genetic variant sharing becomes mandatory?

Let's start with the positives: when we talk about sharing genetic variation data we are standing on the shoulders of giants. We have the human genome assembly,^{1,2} now at version 38. It is still not formally complete, but represents a framework on which to anchor the majority of genetic loci. We also have genome variation descriptions in forms familiar to clinicians (HGVS nomenclature) and to basic geneticists (VCF) and databases like LOVD that can work with both systems. Because the scale of data output from modern sequencers it is becoming self evident that an essential way of attaching meaning and value to those data will be to share the variant information both from other cases and from different centres. Much of this can be obtained from international resources like HGMD, Exac and ClinVar, but some of the data may be associated with clinical records, so whilst sharing can and does benefit patients, especially those with rare variants of unknown significance, it must be done in a way that protects patient and research confidentiality.

As laws and medical practice affecting data sharing are country-specific; national networks are a logical way forward. Australia has taken steps in this direction with a national database (see variome.info) roughly analogous to DMuDB, open to registered participants with 12 participating labs, over 30,000 instances and over 900 unique variants recorded. But it is a sobering thought that even a single exome case would generate 20 to 100-fold more variants. Incentivising labs to share their data has never been easy. It is often seen as an additional overhead for services already under pressure. Yet participation in national networks could become a requirement for laboratory accreditation in Australia and

elsewhere and we will be following developments overseas with interest. Accreditation will push the database from a laboratory filing system into the realm of medical information, subject to quality control and assessment as discussed recently by a joint group from the Human Variome Project and the Royal College of Pathologists of Australasia.³ Although much of this work may need to take place within a national framework, international data sharing standards would ensure the option of wider data exchange where appropriate, aligning with the vision of the Global Alliance for Genomics in Health.

We hope that genetics services across the world will take the advice expressed by our colleagues from Exeter and get a head start in genetic variant sharing.

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Next-Generation Sequencing for Infantile- and Paediatric-Onset Genetic Disease: Evolution of the Leeds Approach

Ian R Berry, Yorkshire Regional Genetics Service.

Of the many challenges that the next-generation sequencing (NGS) revolution has posed to diagnostic service laboratories, the choice of gene enrichment technique has perhaps generated the widest range of solutions across the discipline. In Leeds, we have developed services using a three-pronged strategy (see table 1) to give the best balance of cost, coverage and scalability in different disease modalities. This is best illustrated by the evolution of our infantile and paediatric non-cancer disease services.

Validation of NGS in 2009, based initially on long-range PCR amplification of target genes, library preparation and sequencing on the Illumina GALIX, led to migration of cancer services (BRCA, Lynch syndrome, FAP, Li Fraumeni syndrome, Pheochromocytoma) to the Illumina platform and the first diagnostic NGS reports in the UK. We subsequently introduced services for paediatric-onset neurological and ocular disorders (optic atrophy, familial exudative vitreoretinopathy, cerebral malformations), capitalising on local clinical and research expertise. By the end of 2010, over two-thirds of our laboratory's workload utilised this approach.

PCR-based target enrichment has been highly successful at reducing hands-on and analysis time,¹ and remains the cheapest and most efficient solution for targets requiring fewer than 20 long-range amplicons. In the hands of others, analogous multiplex short PCR and digital PCR approaches (Fluidigm, Raindance, Multiplicom etc.) have been similarly fruitful.

However, it soon became clear that this approach lacks scalability, can introduce amplification artefacts, and, perhaps most crucially, can be severely affected by inter-sample variability in extraction and resuspension protocols (a particular problem for labs receiving a wide range of out-of-area and overseas referrals). A recent comparison of our PCR- and hybridisation-based targeting protocols for 19 different genes across eight typical samples revealed a mean exonic 'drop-out' rate of 6.4 exons for the PCR approach, and only 0.8 exons for a hybridisation-based approach (Agilent SureSelect). Further scrutiny of the exon failures indicated a far more consistent pattern of sample-to-sample coverage in the hybridisation-based libraries, with coverage deficiencies present in just three different exons, compared to 14 different exons in the PCR-based method.

Development of hybridisation-based targeting techniques began in Leeds in 2011. Following comparison of the Agilent SureSelect and HaloPlex chemistries, we began diagnostic work-up on SureSelect, as it offered better on-target coverage, reduced inter-sample variability, and reportedly delivered more accurate allele ratios/fewer PCR duplicate artefacts. Our first development was a service for all 82 heritable cancer genes,² from which phenotype-specific sub-panels can be selected on referral. The first diagnostic reports were issued in April 2013.

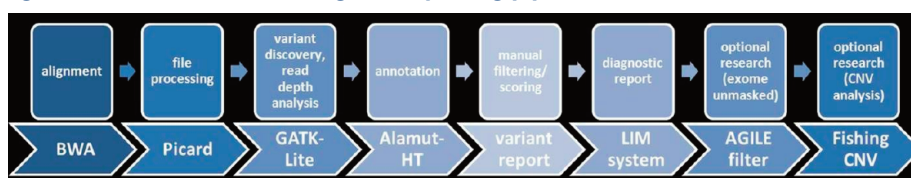
We are now developing diagnostic services for paediatric- and infantile-onset disorders

on two different SureSelect reagents, both run on our Illumina HiSeq pipeline.³ Firstly, a custom panel of approximately 400 genes of local clinical interest, the Selected Gene or 'SelGen' panel (alternative working titles included 'YourGene' and 'Leeds-ome'...), which is ideal for selective analysis of phenotypically-defined, static panels of 2-50 genes. Secondly, targeted gene analysis of whole exomes. The analysis and reporting pipeline is summarised in figure 1. The disease panels currently offered or undergoing validation are summarised in table 1.

Use of this two-pronged approach has several advantages. The smaller custom 'SelGen' panel is somewhat analogous to a clinical exome (a third approach which we are currently validating), but offers reduced sequence run costs (less than half of our anticipated clinical exome sequencing costs) and more comprehensive coverage (of the 734 exons covered in the diagnostic services validated thus far, 730 [99.5%] are consistently covered to a read-depth of 30X in all samples tested). Focussing on a smaller subset of the clinical exome allows us to "play to our strengths" of clinical and scientific expertise (specialising rather than generalising). It also avoids the unnecessary amplification of 4000+ genes, the vast majority of which cause vanishingly rare diseases unlikely to ever be encountered in the clinic, with the associated implications of cost and potential incidental findings. We have designed the gene list such that we can easily expand our current service portfolio into related areas of interest.

In contrast, whole exome sequencing (WES) is applied to highly heterogeneous and/or rapidly evolving areas of genetic disease. With our local interest in recessive ciliopathy disorders, we have focussed thus far on primary ciliary dyskinesia (PCD) and the overlapping Meckel and Joubert syndrome phenotypes, offering targeted panels for each.

Figure 1: Illumina data handling and reporting pipeline.



“By the end of 2010, over two-thirds of our laboratory’s workload utilised [NGS]”

Targeted WES offers two considerable advantages over clinical exome for such disorders. Firstly, the data can be re-analysed in future years in the light of newly characterised causative genes. Since the start of 2013, the number of causative PCD genes has increased from 17 to 32, a rate of discovery by no means unusual in the genomic era, potentially rendering more specific capture reagents obsolete as soon as they are designed. An apparently costly whole exome analysis can eventually look inexpensive compared to repeat applications of an evolving targeted reagent over the course of several years! Secondly, with a large proportion of the genetic component of many paediatric constitutional disorders still undiscovered, the data can be ‘sign-posted’ (with appropriate consent) to specialist research groups for potential discovery of new causative genes once the clinical gene panel is exhausted, offering families the maximum possible clinical yield from one test.

The WES approach has been successful for PCD and Meckel/Joubert referrals; three new presumptive PCD genes have been identified wholly or partially due to research work conducted on the diagnostic exomes^{3,4,5}; two causative copy-number variations were identified in the Translational Genomics Unit, and overall diagnostic yield (see figure 2) so far exceeds 40% for both services.

The Translational Genomics Unit in Leeds have also made some initial forays into the brave new world of WES analysis for a broader range of mixed referrals, with the diagnostic laboratory confirming positive cases through our defined pipeline and producing interpretive variant reports.

For further information on the diagnostic services listed in table 1, please see our website <http://www.leedsth.nhs.uk/a-z-of-services/molecular-genetics/> or contact us directly at leedsth-tr.dna@nhs.net.

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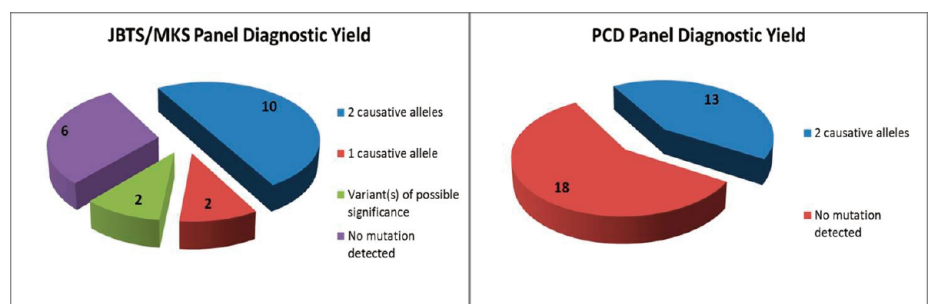
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Table 1: Paediatric and infantile-onset disease services offered in Leeds.

The local areas of clinical and scientific expertise include paediatric neurology (particularly brain malformation disorders), ophthalmological disease, and locally-prevalent rare recessive neurological and developmental disorders, particularly ciliopathies. We also work closely with the Leeds-based national Malignant Hyperthermia (MH) Unit to offer diagnostic MH screening. Developing areas of interest include neurological metabolic disorders (such as cerebral creatine deficiency and leukodystrophy disorders). Services with an asterisk (*) have been approved for national provision by UKGTN.

Panel size:	# of genes:	Gene enrichment method:	Details:	Analysis:	Panels available:	Cost to user:
Small	1-10	Long-range PCR	2-22 amplicons, custom design	Alignment, annotation & variant reporting on NextGene (SoftGenetics), scoring on custom spreadsheets.	Cerebral Malformation (8 genes*) Familial Exudative Vitreoretinopathy (FEVR; 5 genes*) Optic Atrophy (OPA1*) Aicardi Goutieres (AGS, 6 genes*)	£530
Medium	~5+	Hybridisation-based (Agilent SureSelect)	411 selected genes, custom reagent	Internally-developed alignment, variant calling & annotation pipeline. Variant filtering, coverage calculation & scoring on custom spreadsheets, against pre-defined target gene list. Dosage analysis undergoing primary validation.	Cerebral Malformation (16-25 genes) Aicardi Goutieres (7 genes) Pontocerebellar hypoplasia (9 genes) Malignant hyperthermia (MH; 2 genes*) Creatine deficiency (3 genes, April 2015)	£530
Large	25+	Hybridisation-based (Agilent SureSelect)	Whole exome		Meckel* & Joubert syndromes (25+ genes) Primary Ciliary Dyskinesia* (19+ genes) Re-analysis & research project "sign-posting" as required	£1,250

Figure 2: Diagnostic yields of targeted exome panels (including translational research findings); 50% for Joubert/Meckel syndrome (JBTS/MKS) panel, 42% for primary ciliary dyskinesia (PCD) panel.



Conference report: The A to Z of Sudden Cardiac Death

Caroline Sarton, Oxford Medical Genetics Laboratory.

The beautiful Royal Institute of British Architects building in London was the venue of the 5th Annual Cardiovascular Sciences Research Centre meeting on Friday 28 November 2014. The focus of this meeting on sudden cardiac death was particularly relevant to the Oxford Medical Genetics laboratory as it launches a new arrhythmia panel, specifically aimed at individuals with normal post mortem findings.

First of all we heard from Professor Mary Shepherd, in charge of the Cardiovascular Pathology Unit at St George's, University of London who has established an international referral centre for sudden cardiac deaths in the young. Mary gave us a detailed overview of the causes of sudden cardiac death and how these cases are managed. The Chief Coroner, a legal position, is now responsible for referring all cases onto St George's.

Registration of sudden cardiac deaths has yet to be systematically carried out. This is another step towards changing the handling of these cases and improving survival rates. Families receive a detailed report of the findings within 14 days of referral.

The unit is compliant with the Human Tissue Act and is capable of storing the spleen and heart when regional genetics laboratory may not have the ability to do so. Autopsy budgets are astonishingly low (just £97) meaning that histopathology examinations and genetic testing has not previously been readily available.

The incidence of sudden cardiac death (SCD) differs across international borders. Whether this is attributable to

ascertainment bias or genetic differences remains to be seen. Dr Todd indicated in his talk that the incidence of SCD barely varies with social economic status in the UK. However, in the USA there is a marked difference; with people of a low socio-economic status being significantly more likely to suffer sudden cardiac death.

Professor Jacob Tfelt-Hansen outlined an idea from Denmark: to make autopsy mandatory in sudden cardiac death cases. Cost is a major bar to the implementation of this practice, even though family screening savings would make this cost effective at a national level. As Professor Arthur Wilde later outlined, family screening dramatically increases the clinical sensitivity of genetic screening and saves lives.

Lia Crotti, an internationally renowned expert in the genetics of arrhythmogenic disease discussed the genetic detection rate in channelopathy genes. In particular the recently associated CALM1, CALM2 and CALM3 which are responsible for a clinical overlap syndrome of CPVT and LQTS with a severe young onset presentation. Professor Connie Bezzina, professor of molecular cardiogenetics, AMC outlined the problems associated with making a genetic diagnosis in Brugada Syndrome. Brugada Syndrome accounts for about 4% of UK SCD cases. SCN5A is responsible for monogenic disease in about 20% of cases, no Brugada causative genes have been identified by linkage and problems with low penetrance, variable expression and non-segregation make the elucidation of the remaining genetic components difficult. Brugada Syndrome is now moving to an oligogenic model but more data is needed to resolve the background

rate of genetic variation across arrhythmogenic disease and access to well phenotyped cohorts would be invaluable. Until then, data interpretation and genetic counselling will remain challenging.

The clinical side of these diseases was expertly covered; the problems of distinguishing between an athlete's and an affected individual's heart especially in ethnic minorities in ARVC and the cardiomyopathies, problems with delayed resuscitation and new innovations in implantable cardioverter-defibrillators (ICDs). It also transpires that two clinical entities are no longer thought of as causing pathogenic disease; Early Repolarisation Syndrome and Short QT syndrome.

For those of you not fortunate enough to attend, the lectures are available via www.cardiovascular-sciences.org. There was no charge for conference attendance leaving hard pressed NHS trusts to cover travel and study leave only. This was thanks to some very special sponsors: Boston Scientific, Biotronik, Aspetar, Virgin and the charity, Cardiac Risk in the Young.

Cardiac Arrhythmia Multi Gene Panels launched in Oxford

Caroline Sarton and Karen McGuire, Oxford

The Oxford Medical Genetics Laboratory has provided molecular genetic testing for cardiac arrhythmia for over ten years. During this time, it has seen its portfolio of services grow with advances in methodology from screening of single genes through to the highly successful five gene screen. Now, the lab is delighted to announce the launch of three new, more comprehensive, cardiac arrhythmia services using massively parallel sequencing technology. This technology has been part of routine practice in this department since 2011 and the cardiac arrhythmia panel follows on from the large cardiomyopathy panel announced last year.¹

The term 'cardiac arrhythmias' encapsulate a heterogeneous group of diseases that affect the electrical conductance of the heart, and are characterised by distinctive changes on electrocardiogram (ECG): Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is characterised by adrenergically mediated polymorphic ventricular tachyarrhythmias; Long QT syndrome is characterised by a prolonged QT interval on ECG; and Brugada Syndrome (BS) is characterised by ST-segment elevation on ECG, incomplete right bundle-branch block, and ventricular fibrillation (VF). Clinical differentiation of these conditions can be difficult, especially in atypical cases. Sometimes, these changes may only become visible under specific environmental circumstances e.g. times of stress (such as exercise, loud noises or emotional turmoil), during rest or pharmacological stimulation.

The arrhythmogenic disorders can be attributed to a monogenic cause in up to 50% of cases, which are usually inherited

Table 1: Summary of Brugada syndrome, CPVT and Long QT syndrome panels.

✓ = Included in panel.

✓✓ = Key domains guaranteed to be covered by >30 reads or by Sanger sequencing.

✓✓✓ = Coding region guaranteed to be covered by >30 reads or by Sanger sequencing.

Gene	Brugada Syndrome	CPVT	Long QT syndrome
AKAP9			✓
ANK2			✓
CACNA1C	✓		✓
CACNA2D1	✓		
CACNB2	✓		
CALM1		✓	✓
CALM2		✓	✓
CALM3		✓	✓
CASQ2		✓	
CAV3			✓
DLG1	✓		
GPD1L	✓		
HCN4	✓✓		
KCND3	✓		
KCNE1			✓
KCNE2			✓
KCNE3	✓		
KCNE1L (KCNE5)	✓		
KCNH2			✓✓✓
KCNJ2		✓	✓
KCNJ5			✓
KCNJ8	✓		
KCNQ1			✓✓✓
RYR2		✓✓	
SCN1B	✓		
SCN2B	✓		
SCN3B	✓		
SCN4B			✓
SCN5A	✓✓✓		✓✓✓
SLMAP	✓		
SNTA1			✓
TRDN		✓	
TRPM4	✓		
Est. Clin. Sensitivity:	32-42%	50-65%	40-70%
Price (UK & Ireland):	£655	£655	£655
Price (Overseas)	£786	£786	£786
Bespoke Test	POA		

in an autosomal dominant manner. Incomplete penetrance and variable expressivity are key features of these disorders and the phenotype within a single family can range from relatively

benign to sudden death. As such diverse presentations can be seen within a family, molecular testing of 'at-risk' family members has far greater utility in determining which relatives require life-long clinical screening and management.

The new cardiac arrhythmia genetic screening panels have been designed with careful consideration of the available literature and offer increased clinical sensitivities compared to the previous five gene screen for LQT and single gene screen for BS (see Table 1). The CPVT panel is a new test to this department. The genes included on these three panels come together to form a molecular autopsy panel of 33 genes, which would be considered for Sudden Cardiac Death (SCD) individuals with no signs of structural heart disease. The laboratory has had success analysing DNA extracted from archived paraffin block samples, which opens up the possibility of genetic testing for 'old' cases. The technical basis for this test is Agilent's HaloPlex Target Enrichment System combined with Illumina's MiSeq Personal Sequencer and this technique has been shown to work with the small DNA fragments available from paraffin blocks.

The laboratory uses a bespoke in-house pipeline, 'HAPPy', for data analysis which allows greater flexibility for analysis of alternative gene combinations such that we would welcome requests for other combinations of genes from within the panel of 33 genes for rare and unusual cases. The laboratory will continue to offer screening by Sanger sequencing for Timothy syndrome, which includes the common variants responsible for classic and variant Timothy syndrome as well as the newly discovered variant, c.3497T>C p.(Ile1166Thr), in CACNA1C.²

Genetic Technologist Training Day, Bristol 20th November 2014

Emma Clark, Sheffield Children's NHS Foundation Trust

Referrals for all of these services are accepted from Clinical Geneticists, Cardiologists or other relevant medical specialists (in liaison with Clinical Genetics). A fully interpretive clinical report will be issued within 60–80 days. Faster turnaround times may be available in cases of clinical urgency - please contact us directly. For further information, please visit the laboratory website (<http://www.ouh.nhs.uk/geneticslab>) or use the contacts below. Feedback from service users will be gratefully received.

Laboratory Contacts:

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E-mail: Caroline.Sarton@ouh.nhs.uk or
OxfordCardiac@nhs.net;

Karen McGuire,
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Clinical Lead:

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

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Following a brief hiatus during which the ACC and CMGS merged, a training day for technical staff working within genetics was held last month. The event was arranged via the Workforce Development Committee and was supported by the ACGS.

Over 80 people attended, with the majority of genetics labs and a variety of technical job roles being represented.

The morning consisted of introductory talks on joining the ACGS and registration, followed by discussion forums. Groups were split according to what section they worked in and held focussed discussions on key points such as training, registration and quality.

These forums also provided a chance to discuss methods, kits and equipment with colleagues from around the country. The forums were lively and well engaged with, and were a great opportunity for networking.

In the afternoon session there was a series presentations delivered by technical staff on a range of subjects across the whole of the discipline. The talks were well thought out and well delivered – I have since received feedback commenting on the high quality of the talks.

Overall feedback from the day has been very positive, the day generated a lot of interest and enthusiasm from the technical staff and I am hopeful that we can continue to hold such events in future.

May I take this opportunity to once again thank all the attendees for their part in making the day such a success, in

particular our presenters and forum facilitators. I would also like to thank the ACGS, especially the WDC, for all their support in getting this day up and running – it is clear that it the event was very well received and much appreciated by all who attended.

Slides from the day will shortly be uploaded onto the ACGS website, as will a summary of the feedback and discussion forums.

The postman never rings twice

Carolyn Tysoe, Andrew Parrish, Christine Parkes and Sian Ellard, Exeter

In 2006, a Devon postwoman was found guilty of stealing more than 8,200 letters and parcels which were stored at her house over a period of six years. I can't help thinking that this might be a common occurrence underlying the reason behind the number of e-mail and telephone calls we receive from clinical teams requesting copies of reports that were written and posted weeks, months and even years ago! In the modern digital age it seems crazy not to adopt a more efficient approach and to cease sending such vitally important information via letter with the associated risks of being stolen by postpeople!

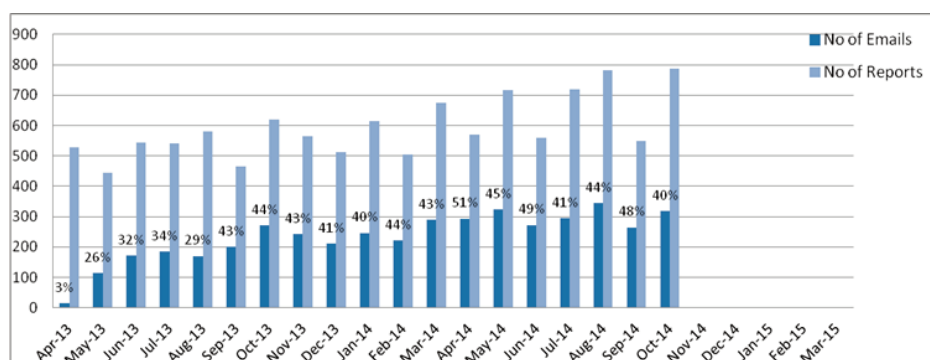
In Exeter, we operate a paperless Laboratory Information Management System (LIMS) so we set out to facilitate the secure transfer of clinically-actionable information in the form of a clinical patient report using electronic means with the added benefits of providing a result to the clinical team two to five days faster while saving on paper, postage and administrators time. Following a period of development with our LIMS provider, StarLIMS, we implemented a system to facilitate the distribution of reports as pdf files direct to an nhs.net personal or generic account in April 2013. Here's the clever bit...briefly: our IT department have set up

an internal relay system to which the StarLIMS system forwards the outgoing emails. This transfer is not encrypted, but is entirely contained within our local network, and the relay system then forwards the outgoing emails to the intended recipient via the NHS.net mail system. This transfer is obviously external to our trust, and is therefore encrypted using TLS authentication (naturally!). A really-good read produced by the HSCIC called 'NHSmail with applications V.7' published in July 2013 details what any local IT department would need to go through in order to establish a similar local relay for other StarLIMS users. In addition, there were a few local changes required to scripts within StarLIMS to set the email options/content as we required. Our Bioinformatics STP trainee Andrew Parrish (andrew.parrish@nhs.net) would be happy to go through these in more detail with relevant personnel if any other laboratory using StarLIMS requires assistance.

We have offered the option to receive reports electronically to several referral centres systematically on a case-by-case basis over the past 19 months and uptake has been positive with an average of 50% of reports currently being e-mailed (Figure 1). However, not satisfied with this, we are constantly

seeking to increase the electronic traffic and save trees, so please contact our Lead Administrator, Christine Parkes, if you wish to receive copies of our reports via nhs.net (via our generic nhs.net e-mail account rde-tr.moleculargeneticsadmin@nhs.net also available on our website www.exeterlaboratory.com/molecular-genetics/).

Figure 1: Number of reports issued by e-mail (dark blue) as a percentage of total reports issued (light blue)



Feedback on the FRCPath Part 1 examinations in Clinical Cytogenetics and Molecular Genetics 2014

Carolyn Campbell, Oxford University Hospitals NHS Trust, Stephanie Allen & Graham Fews, Birmingham Women's NHS Foundation Trust, and Sally Cottrell, Great Ormond Street Hospital for Children NHS Foundation Trust

There were 23 candidates who sat the Part 1 FRCPath written examination held on 25th March 2014, 11 candidates sat the Part 1 written examination in clinical cytogenetics and 12 candidates sat the Part 1 written examination in molecular genetics. The pass rate for the cytogenetics exam was 73% and for the molecular genetics exam was 83%. This was the second year that one of the essay papers had been replaced by a paper of short answer questions (SAQs), and this year candidates sat the essay paper 1 in the morning and the SAQ paper 2 in the afternoon. The SAQ paper consisted of 20 SAQs to be attempted in 3 hours, which approximates to 9 minutes per question. Each SAQ has a stem and 6 sub-questions, is worth 20 marks in total, and is focused around a particular subject area (eg cystic fibrosis, array CGH, colon cancer, GWAS, chronic myeloid leukaemia). Time management appeared to have been less of a problem for candidates with the SAQ paper this year and the guidance given to candidates relating to how much detail is required when answering the questions was followed by most. This year five of the SAQ questions were common to the cytogenetic and molecular papers, and for the first time the essay paper was exactly the same for the Cytogenetics and Molecular Genetics exams. The comments on the essay paper questions for both disciplines are summarised below:

1. Non-invasive prenatal testing (NIPT) for aneuploidy and non-invasive prenatal diagnosis (NIPD) for single gene disorders will revolutionise prenatal screening and diagnosis of genetic conditions. Discuss.

This question was answered by all of the candidates sitting both exams, and in

general was answered well. The most common problems in failed essay questions were insufficient factual detail and failure to answer all parts of the question.

2. The validation and verification of methods is a formal requirement for accreditation according to the standards applicable to genetic testing laboratories. Explain the difference between validation and verification, giving examples of how you might go about each of these with respect to specific laboratory testing protocols.

This question was answered by all candidates sitting the cytogenetics exam and 10 out of 12 candidates sitting the molecular genetics exam. Some candidates lost marks because they did not give examples, and some didn't correctly explain the difference between validation and verification as requested. In particular, there was a lack of understanding of verification and failure to provide appropriate examples of the verification of protocols.

3. Bioinformatics tools and external genetic databases have become increasingly important resources to diagnostic laboratories. Critically evaluate their use and limitations illustrating your answer with examples of each relevant to clinical cytogenetics and molecular genetics.

This question was answered by 10 out of 11 candidates sitting the cytogenetics exam and all of the candidates sitting the molecular genetics exam. The most common problems in failed essay questions were focussing on a very limited number of databases and lack of detail relating to limitations of their use. Some

candidates only wrote about bioinformatics tools OR databases, not both, so lost marks.

4. Discuss the impact that next generation sequencing will have on the delivery of genetics services over the next five years. What are the challenges and opportunities associated with the introduction of this technology?

This question was answered by all candidates sitting both exams. The question was answered well and the majority of candidates achieved a pass mark for this question. Lack of sufficient technical detail and failure to cover the challenges associated with this technology were the main reasons for failure.

5. What is the definition of a rare disease? Why is it important to have a strategy for diagnosis and treatment of rare disorders, and in what areas will genetic testing impact on this strategy both now and in the future? Illustrate your answer with specific examples.

This question was only answered by two candidates sitting the cytogenetics exam and two candidates sitting the molecular genetics exam. The question was not answered well as candidates failed to address all parts of the question asked.

There were 24 candidates who sat the Part 1 practical examination in Autumn 2014 - 10 candidates in clinical cytogenetics and 14 candidates in molecular genetics. The pass rate for both examinations was 100%.

In remembrance of Dr Kevin Ocrafft

Nottingham Cytogenetics Department



Kevin sadly passed away suddenly on Saturday 24th May 2014. He worked in the Cytogenetics Department in Nottingham for 24 years, having earlier studied for his PhD in Nottingham. He had worked in Tameside, St Mary's and Christie Hospitals in Manchester before gaining promotion to the post in Nottingham. Whilst in Nottingham Kevin was in charge of prenatal cytogenetics and was latterly also deputy head of department. Kevin was the most considerate, caring and supportive colleague and boss and it was a privilege to have worked with him for so long.

Kevin was very talented and we miss him professionally in so many ways, his knowledge, his commitment to the service and his sheer hard work, but most of all we miss the person that he was. Almost everyone who came into contact with Kevin would be struck at how extraordinarily helpful and kind he was. Assistance came in many forms ranging

from explaining a complex chromosome abnormality, jump starting a car, resolving the latest IT frustrations to mending a bike puncture late into the evening. All of the help was delivered with great patience and good humour and this undoubtedly ensured that he fostered successful and productive relationships with all that he came into contact with. You could rely on Kevin to show a friendly face with a big smile, he would always make time for you and had genuine concern for everyone's welfare.

Messages sent to the department included time and time again phrases like "a lovely man", "gentle", "kind and generous", "professional", "dedicated", "caring", "thoughtful", "helpful", "a real gentleman"... the list is endless.

In the wider profession, as many will know, Kevin served for three years as the treasurer of the ACC and latterly the ACGS. His conscientious, diligent and knowledgeable approach to this role helped to ensure that this difficult transition period was navigated successfully.

He was a keen cyclist and photographer.

He leaves behind his wife Susan and three children Sarah, David and Lisa.

We miss Kevin being part of our professional lives, but his legacy to the department is that we continue to strive to deliver the best service possible, and keep the patients as the centre of our focus.

CGG News Editors



Deadline for contributions for next issue is 30 April 2015

Molecular Genetics Editor Dr Martin J Schwarz PhD FRCPATH

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Editorial

Whilst reading through the articles for this issue, I was struck by just how much the field of genomics is becoming a reoccurring theme. It seems that the word genomics is becoming more integrated into our vocabulary, and it looks like it will become increasingly assimilated in our roles as genetic counsellors, whether in a clinical or research setting.

This issues AGNC report outlines some exciting new proposals for the future, which embraces our role in genomics education. We also have reports from two conferences from our well-travelled colleagues, and in amongst the programme highlights are presentations on genomics and our role in patient care.

It really is quite a packed section for the AGNC this issue. We have an update from the registration board, outlining the result of the Accredited Voluntary Registration vote, for which the vast majority are in favour. The opinion piece takes a look at the impact of the wealth of information that patients have access to before even seeing us in clinic, and the challenges and benefits that brings. There is a genetic counsellor training panel update, as well as results from the survey looking at the roles of genetic counsellors and nurses in inherited cardiac conditions. I would also like to draw your attention to new publications for parents and patients with sex trisomies that have been developed, and are available from Unique.

Happy reading!

Judith Edhouse

Genetic Counsellor Registration Board (GCRB) update

Diana Scotcher (Manchester) and Barbara Stayner (Oxford), Co-Chairs GCRB

Accredited Voluntary Registration (AVR)

Recently the GCRB asked each Registered Genetic Counsellor if they support the GCRB in submitting an application for Accredited Voluntary Registration (AVR) to the Professional Standards Authority (PSA). The result of the anonymised poll, coordinated by our administrator Chris Barnes, showed overwhelming support for AVR.

Votes were received from 106 registered genetic counsellors (57% of the 186 currently registered).

- YES: n=102 (96% of votes cast)
- NO: n= 3 (3% of votes cast)

(In addition, one vote was declared invalid as a non-valid registration number was given.)

With this strong mandate the Joint Committee on Genetic Counsellor Regulation (JCGCR) and the GCRB will now finalise the application, which will be submitted by the end of 2014.

GCRB website

The application for AVR will be strengthened by the new GCRB website, which will be launched in the near future, and will include an online facility for payment of fees for GCRB registration and renewal of registration. We will inform all genetic counsellors when the website is in action.

GCRB registration and plagiarism software

The use of plagiarism software is being introduced to the registration process from 2015. The documents for using the iThenticate plagiarism software (<http://www.ithenticate.com/>) have been sent to all Sign-off mentors (SOMs) to

discuss with applicants, and these will be available on the new GCRB website in the near future. This development brings the board into line with current practice in most Higher Education Institutions. The GCRB hope that use of this software will not only reduce plagiarism in portfolios, but also improve the scholarly writing style of applicants.

Election of new GCRB members

GCRB elections for new board members took place in September, and as a result Caroline Kirwan, Vishakha Tripathi and Melanie Watson will take up their places on the board in January 2015. The GCRB would like to thank Lorna McLeish, Barbara Stayner and Sally Watts who are stepping down, having now completed their tenure. Barbara, Lorna and Sally have all made important contributions to the work of the GCRB.

Sign-off Mentor (SOM) training

SOM training is arranged annually, and the next course will be in Glasgow on 10 June 2015 after the ESHG conference. All SOMs should attend a training course every 3 years, so remember to plan ahead and ensure that departments have sufficient trained SOMs to support genetic counsellors going through registration. Please contact the GCRB administrator Chris Barnes if you would like to book a place on the course.

GCRB Annual General Meeting (AGM)

The AGM will be on 8 June 2015 at 12.30 at ESHG conference in Glasgow. All are welcome to attend.

New registered genetic counsellors

Congratulations to the following genetic counsellors registered with the GCRB in July 2014.

Association of Inherited Cardiac Conditions (AICC) survey

Liz Ormondroyd (Oxford) and Kath Ashcroft (Leeds)

Jessica Bailey
Emily Clarke
Andrea Edwards
Claire Giffney
Sasha Henriques
Jessica Hensman
Lisa Hughes
Kelly Loggenberg
Jessica Myring
Elizabeth Ormondroyd
Joanna Patterson
Nicola Taverner

Contact the GCRB

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

Inherited Cardiac Conditions (ICCs) are a group of largely monogenic disorders affecting the heart, its conducting system and vasculature. The first indication is sometimes sudden cardiac death (SCD) often in adolescents or early adulthood. A Service Specification for Inherited Cardiac Conditions, including arrhythmia syndromes, cardiomyopathies, inherited arteriopathies, muscular dystrophies and families afflicted by Sudden Arrhythmic Death Syndrome (SADS) was recently published by NHS England¹. The stated aim of ICC services is to improve the diagnosis, treatment and outcome of patients with inherited cardiac conditions, and achieving this aim requires specialist clinical management by multidisciplinary teams including:

"Genetic Counsellors to provide pre- and post- test counselling and to co-ordinate DNA testing, aid in genetic data interpretation and cascade testing of at-risk family members. ICC nurse specialists with training in counselling, and in the evaluation and management of adults and children with inherited cardiovascular conditions".

Since little is known about the employment of genetic counsellors and specialist nurses with ICC services, we undertook a survey on behalf of the AICC to learn who is doing what, and what additional training they consider appropriate.

68 respondents from across the UK completed a ten item survey; 40% were genetic counsellors, and 60% were registered nurses. The registered nurses were especially diverse in terms of background, qualification and roles within services. In addition to working in ICC, many genetic counsellors also carry out

cancer and general genetic counselling, and research. Around two thirds of all respondents would appreciate training in cardiology, while three quarters of nurse respondents would appreciate training in genetics. Counselling training was also endorsed. Respondents elaborated in free text comments that issues specific to ICCs in cardiology, genetics and counselling were important.

We welcome hearing from interested people to form a working party to think about how training might be implemented. Please contact: Liz Ormondroyd (liz.ormondroyd@cardiov.ox.ac.uk) or Kath Ashcroft (kath.ashcroft@nhs.net)

Reference

1. <http://www.england.nhs.uk/wp-content/uploads/2013/06/a09-cardi-inheri-card-con.pdf> (accessed 1.12.14)

European Human Genetics Conference (ESHG) and European Meeting on Psychological Aspects of Genetics (EMPAG) June 2014, Milan: meeting report

Elizabeth Alexander (Manchester Centre for Genomic Medicine)



Enjoying the sites of Milan, during a well-earned break: (from L-R) Kate Brunstrom, Sarah Bennett, Theo Gale, Elizabeth Alexander, Lyndon Gallacher, Debbie Holliday, Sian Jenkins and Helen Jolley

As newly qualified genetic counsellor this was a trip of many firsts; my first conference as a genetic counsellor, my first EMPAG, and my first time co-presenting my qualitative research project.

When starting a four day conference it is impossible to imagine that I could sustain attending all of the sessions, but when looking through the EMPAG programme, it was hard to imagine what I could miss. Whilst many of the sessions evoked the traditional values of genetic counselling, a closer look at the talks left no doubt that the new era of genomic medicine ran through the whole programme. Many of the talks addressed the complexities of offering whole genome sequencing, what to do about incidental findings and how to present and consent our patients to these tests. It is reassuring to see the international community experiencing the same dilemmas, and learning from each other how to approach these issues.

Nevertheless, as a new genetic counsellor I am acutely aware that I am currently developing my basic skills of genetic counselling. The big questions on new technologies and the exciting opportunities they bring, for me at present it is a backdrop rather than the focus of my career. Even from this standpoint there was much to absorb from EMPAG. Speakers addressed the language we use with patients, how to communicate risk, how to support our patients with genetic knowledge, decision making, and how to define a child's right to an open future. These fundamental questions are now being debated anew in the face of the new technologies.

The Saturday plenary session on reproductive decision making highlighted this point. In particular the sessions on decisions around screening for Down syndrome in pregnancy given by Marcia L Van Riper (USA), and Charlotta Ingvaldstad (Sweden). As one of the first conditions identified as having a genetic basis and tested for prenatally since the sixties, one would assume that this was a well-developed area. Van Riper and Ingvaldstad's work showed this is not uniformly the case, and there is still a need to educate around providing parents with pre-test information on Down syndrome to enable informed prenatal decision making.

This begs the question; if this information and education aren't delivered well, what hope do we have as new technologies move in? This reminded me how important it is not to leave the basics behind as we move into this new era. A thought emphasised by one of the most enlightening talks I attended. D.W Bianchi's presentation *Non-invasive prenatal testing creates an opportunity for*

antenatal treatment of Down syndrome, describing how early diagnosis of Down syndrome using Non-Invasive Prenatal Testing (NIPT) could present a window for treatment of the condition. This talk has changed the way I now think about NIPT, highlighting that in genetics you can never stop revisiting the basic understanding of a topic.

The Sunday educational session: *Responding to guilt and shame in clinical consultations* was a particular highlight of mine. During this session Clare Baguley, from the UK Psychological Professions Network, addressed what we know about these fundamental human emotions. She described the normal process of adjustment to new information which affects life decisions, and highlighted how this can become dysfunctional in some people. We watched a powerful role play of a clinic situation which demonstrated how acknowledging and attending to these feelings in a counselling session can help the patient share their feelings which can inform the rest of the session.

So, whilst waiting in the airport for my flight home I found myself reflecting on this trip of many firsts. I was left exhausted but overall enthused by this community I am now part of. I couldn't help feeling that although medical genetics is facing new and exciting challenges, it has been facing similar debates in different guises since the profession was born.

I would like to thank the AGNC for the support to attend and present at this conference.

Challenges and benefits of increasing public genetic awareness

Emma Williams (NE Thames)

As genetic counsellors, our profession is perhaps one that the general public, and to some extent other clinicians, are less familiar with. As a result of this, part of our role has always involved education about what genetic counselling is, to not only our patients but also other health professionals.

Over the last 18 months we have experienced a significant increase in the number of women seeking genetic counselling and gene testing. This was largely following the press coverage about Angelina Jolie undergoing risk-reducing breast surgery, following identification of her BRCA carrier status, which generated much international attention. The updated NICE guidelines in 2013 also included the option for unaffected BRCA testing in certain circumstances.

Increasing awareness is hugely important, especially in the field of cancer genetics, where there are options available for cancer risk reduction or early detection. While our cancer genetics team has seen at least a two-fold increase in referral rates, since the summer of 2013, we observed that the majority of this increase has been for women who would not be considered to be at high risk on the basis of their family history, so consequently would not meet the referral criteria for an appointment in the cancer genetics clinic, let alone a BRCA1/2 gene test on the NHS.

Of those who have been offered an appointment in clinic, we have noticed that an increasing number of patients attend with the opinion that they have obtained sufficient knowledge and understanding about the BRCA genes and gene testing prior to the appointment, and view genetic counselling as a gate-keeping process for testing.

With the internet and social media being a primary source of information for a growing proportion of our population, this is hardly surprising. However there is such a breadth of unmonitored information that is readily available on the internet, and also from peers through online support groups/forums, my concern would be that patients sources of information may not always be that accurate and reliable.

It has been my experience that this has led to a number of more challenging genetic counselling consultations, when a patient who considers themselves to be well educated about the genetics of breast cancer, has actually been misinformed or misunderstood the nature of an appointment in a cancer genetics clinic or BRCA gene testing.

As an experienced cancer genetics counsellor, I am used to explaining the reasons behind a decision not to offer gene testing to an unaffected patient when they do not fulfill the criteria, and explain the complexity and possible limitations of interpreting a BRCA testing in unaffected patients.

I have more recently encountered a small minority of patients who are certain that they are entitled to a gene test, irrespective of my explanations, the belief of which may have been initiated by a referring clinician. Managing these expectations can be very difficult.

I would imagine that this type of experience is not unique to our department, and that other genetic counsellors throughout the UK may be facing similar challenges. I think it highlights how important it is that we continue with our role as educators to both patients and clinicians to try and align expectations with what we can offer as

much as possible. This is particularly important as recent developments in sequencing technology and the decreasing cost of testing, mean the complexity of genetic information that is available to patients is almost certain to increase in the near future.

Conference report: The International Society of Nurses in Genetics (ISONG) World Congress on Nursing and Genomics, November 7th-9th 2014, Scottsdale, Arizona, USA

Caroline Benjamin (School of Health, University of Central Lancashire)

Scottsdale is located in the Salt River Valley, also known as the 'Valley of the Sun'. During my stay it lived up to its name with average daytime temperatures of 26C.

I have been involved with ISONG for a number of years and the UK has demonstrated international leadership with past presidents including Professor Heather Skirton and Professor Maggie Kirk.



Caroline getting to know the locals, Scottsdale, Arizona.

I was fortunate to be an invited session speaker to present *The scoop on our scope; what's new with the scope of practice for genetics nursing*, and also delivered a research abstract presentation *Interdisciplinary working, workforce utilization and referral management: results of a prospective study*. The meeting was attended by 250 registrants, representing ten countries. It consisted mainly of nurses practising as advanced practice genetic nurses (APGNs), nurse educators and researchers. A diverse programme included 82 spoken sessions and 25 posters.

The first day's keynote was delivered by Margaret Heitkemper, Professor of Nursing at the University of Washington. She described the US National Institutes for

Nursing Research development of the 2013 *Blueprint for Genomic Nursing Science* www.ninr.nih.gov/genomicsblueprint. This explores ways to further genomic nursing science to improve health outcomes for patients. It also provides grant funding for nurses wishing to conduct genetic or genomic research. She stressed that, "nurses are with the patient and family during and after genetic information is shared". Many nurses in the US are involved in translational research projects ranging from biological laboratory science through to psychosocial genetic and genomic issues. Her own work focuses on determining if there is an inherited predisposition to Irritable Bowel Syndrome.

A symposium later that day focused on *Jump Starting your Career in Genetics as a Nurse Scientist*, with presentations from Taura Barr and Jacquelyn Taylor. Both are nurses running their own laboratory research into diseases such as hypertension, stroke and symptom characterisation. Other presenters



Susan Wesmiller, Assistant Professor, Health Promotion and Development, University of Pittsburgh presenting an ISONG Research Grant to Caroline Benjamin.



Downtown Scottsdale

discussed how nurses could participate as part of larger interdisciplinary research programmes, and were needed to retain focus on the patient and the family.

Choosing just one of three concurrent sessions to attend over the next couple of days proved difficult. I found *Case studies to enhance education*, most inspiring. Here Kathleen Calzone presented the Global Genetics and Genomics Community (<http://g-3-c.org/en>) use of on-line simulations for teaching. This demonstrated to me how far US teaching resources have developed over the last few years. Maggie Kirk showed videos of the genomics teaching at the University of South Wales and their pioneer use of drama, where students act out characters in an unfolding story. Concurrently more traditional concepts such as culture and genetic testing were an option, with presentations from Israel, Columbia and Brazil.

On the second day I attended the sessions relating to genomics education. Karen Whitt and Delwin Jacoby both presented on-line courses they had developed at their own Universities to integrate genetics and genomic teaching into the nursing and allied health professional curriculum. Others presented the development of

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Peter Marks, AGNC secretary (Birmingham)

instruments to measure genetic literacy prior to and after educational interventions, such as the Genomic Nursing Concept Inventory (Linda Ward).

The *Genomics in Practice* sessions over the two days concentrated on clinical practice settings such as perinatal, cancer genetics and genomics and chronic disease. There was an excellent presentations by patient support group FORCE (Facing Our Risk of Cancer Together)

(<http://www.facingourrisk.org/index.php>) showing the benefit of this information source for patients. Also the development of an App to increase BRCA provider knowledge at point of care.

The ethical, legal and social issue keynote was presented by Malia Villegas, Director of the National Congress of American Indians. This was enlightening regarding the involvement of these groups in historical and ongoing bio banks, including genetics research. She explained how the saying "walk softly, listen carefully" guided their work in facilitating an understanding of cultural issues between researchers and participants.

The full programme and details of the organisation is available from <http://www.isong.org>. I would encourage UK nurses, counsellors and those interested in clinical practice, education or research to consider joining this international organisation or attend the Congress in Pittsburgh next year. It provides opportunities for education, research collaboration and professional development.

I would like to thank the AGNC for providing a travel grant, which enabled me to attend this meeting.



The AGNC committee November 2013: (from L-R) Liwsi-Kim Protheroe-Davies (Swansea), front- Cath King (Bath), back- Anita Bruce (GOSH), Oonagh Claber (Newcastle), Peter Marks (Birmingham), Claire Giffney (Birmingham), Laura Boyes (Birmingham).

Since the 100,000 Genomes project was announced in 2012, the clinical genetics community has been awaiting details of how we will be involved in this most ambitious government initiative. 2014 has seen Genomics England Limited (GeL), the Department of Health-owned company responsible for delivering the project, stage a series of events and presentations around the country aimed at educating health professionals and the public alike about the potentially very exciting legacy for genomic healthcare in the UK.

Committee and other members of the AGNC have been lobbying GeL throughout 2014 to promote genetic counsellors as versatile clinicians uniquely placed in the NHS not only to help recruit patients into the project and provide specialist care to those families impacted upon by findings but also to assist in training the mainstream workforce in aspects of genomic medicine. The AGNC vision statement, available on our website

and discussed in the last newsletter, was certainly developed with this in mind.

We have also been liaising with Health Education England, which will be co-ordinating workforce training and planning in anticipation of 100,000 Genomes. As a result of this engagement, together with representatives from the Genetic Counsellor Registration Board (GCRB), Joint Committee on Genetic Counsellor Regulation (JCGCR), lead genetic counsellors, and the Genetic Counsellor Training Panel (GCTP), an opportunity to transform genetic counsellor training and funding has been presented. Discussions about this are at a very early stage but one possible option being considered is an intercalated, funded, MSc and training post scheme along the lines of the NHS Scientist Training Programme. Clearly, this would be a major change from the current training routes and any forthcoming details will be carefully scrutinised in the interests of our profession.

In anticipation of our likely role in genomics education of the mainstream workforce, the committee is strongly committed to promoting the up skilling of UK genetic counsellors in the fields of genomics and bioinformatics. The forthcoming ESHG meeting in Glasgow in the spring of 2015 will feature a number of key sessions around these subjects, and the AGNC committee has decided to offer funding grants enabling one member from each genetics centre to attend this meeting. It is expected that the lead genetic counsellor from each centre will submit an application on behalf of their nominated genetic counsellor. The Wellcome Trust *Genomic Counselling for Genetic Counsellors* course in July 2015 at Hinxton, will also help to ensure that genetic counsellors are prepared for advances in the field of genomics.

In other news, the committee is continuing its work into sharing genetic counsellor practice nationally and will be conducting a pilot survey of practice around predictive testing for adult onset conditions for which treatment and/or surveillance is available. It is anticipated that surveys will be completed by the lead genetic counsellor from every genetics centre in the UK in order to provide a snapshot of current practice. The findings will be published by the committee in the summer of 2015.

We would like to thank Oonagh Claber and Cath King for their terms serving on the committee. Oonagh recently served as secretary and Cath as treasurer. Their hard work has been much appreciated. We now welcome their successors on the committee, Pam Harris and Anna Middleton. We also say thank you and goodbye to Claire Giffney, who has completed her term as the new genetic counsellor representative and who is

succeeded by Helen Jolley. We welcome Helen and look forward to working with her.

Finally, I would like to take this opportunity to remind all members that AGNC membership is free for student genetic counsellors (though a discounted BSGM annual subscription – currently £20 – is required). Do encourage students based in your centres to join so that they can take advantage of the benefits of being a member, be represented, and be welcomed into a professional community of which they will soon be part.

Genetic counsellor trainee meeting 25th June 2014

Claire Dolling (Birmingham)

Genetic Counsellor Training

There are currently two entry routes to become a registered genetic counsellor in the UK:

- Registered nurse or midwife with at least two years post registration experience and additional counselling and genetics training.
- Graduate from one of the two UK based MSc Genetic Counselling programmes, accredited by both the UK Genetic Counsellor Registration Board (GCRB) and the European Board of Medical Genetics (EBMG).

Two years of supervised clinical training then provides sufficient experience to fulfil competencies for genetic counsellor registration. Following the 2003 (Department of Health) DH white paper, "Our Inheritance, Our Future" the DH provided funding for 50 trainee genetic counsellor posts. This centralised funding has now ceased, with reliance instead on departmental budgets to fund this training period.

The AGNC is actively pursuing options to secure centralised funding for future high quality genetic counsellor training, in the UK. Meanwhile, the Genetic Counsellor Training Panel (GCTP) continues to facilitate and monitor posts aimed at training genetic counsellors for registration in the UK and Republic of Ireland.

On 25 June 2014, the GCTP organised a Genetic Counsellor Trainee meeting at Birmingham Women's Hospital. Twenty one trainee genetic counsellors attended from England (16), Scotland (4) and Wales (1). The programme included spoken presentations addressing professional issues such as registration and training,

and a presentation on teaching genetics. There was opportunity for small and whole group discussion and case presentations. Feedback from the day was extremely positive with participants appreciating the opportunity to network and share their training experiences. The case presentations and subsequent discussions appeared to be particularly valued, and provided an opportunity to share good practice.

Genetic counsellor trainees: update

- Departments appear committed to genetic counsellor training, and are supporting this in a variety of ways. Centralised funding would ensure that this is sustainable and help maintain a high standard of training. The AGNC is actively working towards this end.
- The day highlighted the benefits of a learning contract, which is based on registration competencies and is regularly reviewed. The learning contract provides a structured tool to identify an individual trainee's learning needs and help monitor progress. The GCTP actively encourages the use of learning contracts for all new genetic counsellors and is happy to review learning contracts and offer guidance where needed. Information on learning contracts is available in the GCTP section of the AGNC website (www.agnc.org.uk)
- Current new recruits have mainly entered the profession via a scientific background plus MSc in genetic counselling route. We need to consider ways to support and encourage applicants with nursing backgrounds in order to maintain the diversity that nurses and midwives bring to the profession.

- Not all participants were members of the AGNC. Membership of the AGNC is actively encouraged as a way of maintaining currency with professional issues, supporting best practice and delivering high quality patient care.
- The training day was a success and provided participants with a forum to network, gain peer support and share good practice. Participants appeared to particularly value the opportunity to discuss and present cases and to share experiences with their peers. Participants' commitment to structured, competency based training and their desire to share evidence based practice was particularly impressive.
- In light of the positive feedback received, the GCTP plans to organise another training day in 2015. If it is felt helpful, this could include participation from training mentors.

Training panel members

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With thanks to: Claire Giffney, AGNC new genetic counsellor representative, and Antoniya Ruseva, genetic counsellor trainee

Children with sex chromosome trisomies: booklets to help parents tell their child about a diagnosis

Sarah Wynn (Unique, Rare Chromosome Disorder Support Group, Oxted, Surrey), Dorothy Bishop and Gaia Scerif (Department of Experimental Psychology, University of Oxford)

When a child is diagnosed with a chromosome disorder, parents will want to know what the impact will be for the child and the family. Another question that will arise sooner or later is how to discuss the diagnosis with the child and with other people. If the disorder has obvious effects on development, then a diagnosis can be helpful in providing an explanation. Things are more complicated, though, for a condition such as a sex chromosome trisomy (47,XYY, 47,XXX also known as triple X or trisomy X, and 47,XXY, also known as Klinefelter's syndrome). Children with all three trisomies are at risk of educational difficulties, particularly those affecting language and communication, but the range of outcomes is very wide. Most children attend mainstream school and some will go on to university.

Many parents are concerned about whether or not to tell their child about the trisomy. For example, a team of psychologists, clinical geneticists, genetics counsellors and members of Unique found that parents of children with a sex trisomy were less likely to disclose to their child, siblings and school if their child had higher cognitive, social and emotional functioning¹. Those parents who wanted to tell their child also reported that they felt unsure about how to go about doing this.

With funding from the Nuffield Foundation, researchers at the University of Oxford have developed a set of booklets designed to help parents confronted with this issue. They focused on 47, XXX and 47, XYY, because in these conditions there is no good evidence of any effect on sexual development or ability to have children. The issues are more complex in Klinefelter's syndrome, where there are effects on puberty and fertility.

The booklets were designed after surveying parents to find out more about factors affecting a decision to disclose a diagnosis, and ways in which parents had gone about this. The researchers also asked for the views of young people who had 47,XXX or 47,XYY who knew about their diagnosis.

The goal was to produce, for each condition, two booklets. The first one is for parents, and discusses the pros and cons of disclosing the diagnosis. The aim is to give parents information that will help them balance different factors in coming to a decision. For instance, many parents were concerned that if they disclosed the diagnosis, then this could lead to the child being stigmatised. On the other hand, the child might be relieved to have a diagnosis, particularly if it provided an explanation for developmental difficulties.

To help those parents who decide to disclose the diagnosis, the researchers developed a picture book for each condition. This is suitable for children with a developmental level of around 6 to 10 years. It does not explain complex genetics, but focuses on the idea that having an extra chromosome is just one way in which people can be different from one another. It is hoped that if parents start this conversation with the child when they are fairly young, they can then allow understanding to develop more gradually as their ability increases with age.

Printed copies of the booklets for parents and children are available from Unique (please email Sarah Wynn, sarah@rarechromo.org), and the booklets can also be freely downloaded from the web (www.rarechromo.org or on <http://dx.doi.org/10.6084/m9.figshare.1203560>).

Reference

1. The manuscript about current disclosure choices (Gratton, Myring, Middlemiss, Shears, Wellesley, Wynn, Bishop and Scerif, under review) is available upon request (please email Gaia Scerif, gaia.scerif@psy.ox.ac.uk).

AGNC News Editor



Deadline for contributions for next issue is 30 April 2014

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Editorial

Derek Lim

Welcome to the latest edition of the CGS section of BSGM news. What a busy time it has been for all of us in clinical genetics not only in terms of the clinical workload but a lot of us would have also been involved with various aspects of engaging with the 100K Genomes project and the tight deadlines. It is an exciting time to look ahead as we move in to the genomic medicine era. Mainstreaming genetics continues to be on the agenda as well and our president discusses important aspects of our future roles in clinical genetics/genomics. The times are a changing indeed. I couldn't help but create a little cartoon to accompany Jill's letter because of the image that she has conjured up (read on for further details) in my mind.

Many of us would have met or heard Wendy Jones, a clinical PhD student working at the Wellcome Trust Sanger Institute, present her research and her involvement with the DDD project. Wendy has kindly contributed an article about tips and guidance about choosing a PhD project as well as the importance of clinical geneticists to learn to programme to interrogate the big data that we will no doubt receive in the near future. Yes we will have bioinformaticians, but having that added knowledge to our repertoire of skills will be very beneficial.

I am pleased that Mary O'Driscoll agreed to review a selection of available apps for smartphones and tablets that are relevant to genetics including the TGCA app that was developed by some of our members at St George's Hospital. We should embrace the technological advancements in such handheld devices and take the opportunity to utilise them for patient benefit. Instant knowledge accessible at your fingertip is very powerful. Speaking from personal experience, sometimes, it can even save you from embarrassment in an MDT meeting when inflicted with the dreaded brain-freeze moment.

One of the broadening roles of the CGS is to foster international relationships with other genetics centres. One of the ways this is achieved is through the CGS International Scholarship. Dr Neerja Gupta from New Delhi was awarded the scholarship in 2013 and we hear about Dr Gupta's experience in Manchester.

Please remember to keep the date **3 March 2015** in your diary for the upcoming CGS spring conference in London at the Royal College of Physicians. I hope that the registrars/trainees have taken the opportunity to submit an abstract for the Robin Winter SpR Prize and judging by the quality of the presentations in previous years, I am confident that the standards will remain high this year. The trainee report in this edition also highlights the various funding opportunities provided by the CGS and I encourage you to take advantage of this.

Finally, we are very sad to lose a colleague in Birmingham and we feature an obituary on Dr Louise Brueton. On a personal note, I am very proud to have trained under Louise and am very grateful for the guidance and support she has given me throughout my career in genetics. This paragraph was particularly difficult for me to compose without feeling upset but that just goes to show the lasting impact she has on the people she met and the patients she cared for as evident by the tears shed and the very kind words about Louise relayed by her patients who I've met in clinic when informed about her passing. At difficult and sad times like this, we often think about our close family and friends but I would add that we not forget our colleagues around us.
#LifelsShortAndPrecious

Derek Lim

Letter from the President: The times they are a-changing

Professor Jill Clayton-Smith

Change is in the air and don't we know it. Many of you will be suffering from 'tender fatigue' following a busy few months of drafting, site visits and rearranging everything at the last minute to attend meetings. There are so many initiatives underway that it's becoming difficult to imagine just what the role of today's clinical geneticist will be in the future health service. The Lead Clinicians and CGS council met to debate this just recently and sought advice, too, from other specialties of what exactly they would want from us in years to come. We are writing a summary of the full proceedings of that meeting which will be available to everyone in due course. Those who have been pondering just what you will be doing in a couple of years, however, might be interested in a snapshot of the views of our mainstream colleagues from cardiology, oncology and general practice, all of which provoked some interesting discussion.

Our trainees were particularly worried about the change we will have to make from Clinical Geneticists to Clinical Genomicists. It had been remarked by others outside our specialty that that this conjured up a workforce of small people in red hats, not an image we would like to project. But it turns out not to be a major worry, as the mainstreamers we asked certainly didn't think we would all have 'Gone fishing'.

Many mainstream specialties are already conversant with genomics and use it in their everyday practice. They felt that with results from the UK 100,000 genome study coming through, with new genomic discoveries which could influence therapies, and with a new generation of trainees who will be more genomics literate, that they envisage a world where

"as a specialty we need to lead change in the genomics era"

much genomic advice would be given by those working in mainstream specialties. They emphasised, however, that they would need to have a clinical genomicist in their multidisciplinary teams. Ideally they would like us all to subspecialise, learning to "speak their language" and participate in their clinical networks. This is because they see us in an advisory role for more complex cases. They stressed the need for us, working with scientists to provide them with standardised laboratory reports which convey a clear message and are easy to interpret, stressing clinically actionable results. In essence, they see a role for us in clinical interpretation before reports are actually sent out to them. They would also like the genomic medicine service to be there to pick up the pieces for more puzzling or complex cases or where results are more difficult to explain (The term "rescue counselling" came up more than once). They are confident that they can counsel straightforward cases but feel that they have limited abilities to do complex counselling, investigate extended families and recognise dysmorphic features. They are already well versed in clinical trials but can see an increasing role for the genomicist in the clinic trials team.

Perhaps the most eye-opening presentation for us was from Jude Hayward, a GP with a special interest in genetics from Yorkshire. She led us through a day in the life of an average GP and how applying genomic medicine would fit into this. A GP works in time slots of 10 minutes in a paperless environment. Any model for delivery of genomic medicine in primary care has to take this into account but with the innovative use of IT it is possible and GPs do foresee that they will have a role. It

was interesting for us to realise that GPs feel they only have time to learn what is relevant to the case in hand and so not many are likely to opt to go on courses or attend lectures in genomics, as it may be some time before they see a patient with a genomic disorder. Their challenge is how to maintain their generalist and care co-ordinator role whilst learning about new things like genomics. As far as genomics goes, when the situation presents, they want the resources at hand to be able to address this and we saw interesting demonstrations of systems which allowed temporary sharing of electronic clinical records to get advice from specialists and links directly from the GP desktop to pathways for testing and counselling for example in haemochromatosis. Those who have been sceptical about genomic medicine coming to GP-land are undoubtedly wrong. Whilst they would still like us to see complex or rare disease patients they don't see that all of their patients need to be seen face to face and want to speed things up for them by interfacing better with us, with most of this interfacing being done electronically. When we do send letters, they would like these to clearly state a problem list and an action plan so that these key features can be entered as fields onto the GP database rather than less structured letters simply being scanned in.



It's clear that as a specialty we need to lead change in this genomics era. There is no room for us to be precious; we have to make ourselves useful to other specialties as they evolve. The message is that we are "Better together" and we need to heed the request for subspecialisation. We discussed models such as Post-CCT fellowships for mainstream and genomics trainees to become conversant with each other's specialties and support for development of genetic counsellors in specialist areas. Within our own community, clinicians, counsellors and scientists need to deliver genomics together. There will be some other key requirements for our evolving role; access to training in new skills such as bioinformatics for existing consultants, not just for trainees, and importantly, a key need to address the IT deficiencies within our Trusts. Commissioning too will need to address new models where not every patient is seen face to face.

So, trainees, I have done it. I have changed us from geneticists to genomicists within the course of this short article. And in my head, I have changed us from the small men with red hats to something more akin to the little stick man with a reputation for helping that I used to have on my Brownie uniform. Brown Owl knew something all those years ago when she put me in the g(e)nomes.

How to choose a PhD and reasons why Clinical Geneticists should learn to program

Wendy Jones, Clinical PhD student
Wellcome Trust Sanger Institute

Have you ever thought about doing a PhD or MD or do you have a trainee who is thinking about it? Maybe it's time to start exploring options and possibilities?

When embarking on a research project you can't know exactly what you will find (if anything at all), or whether the competition will beat you to it, or all the challenges you will face. What you can do though, is to set yourself up with a good supervisor to cross uncharted scientific territories with and a project that gets you excited, and see where that takes you. But how do you even go about doing that?

Explore: When I was searching for a PhD, many colleagues gave me extremely helpful advice. Speak to as many people as you can, in fact never stop speaking to people about research, science is about sharing ideas and collaborating and this is just the beginning of the journey.

What do you find interesting? Who works on this? Be creative, can you bring your own previous work into a PhD? Don't forget, you can apply for data from the DDD project, what questions could you ask? Visit potential supervisors, or wise people you think might be able to help you. Don't be discouraged if a meeting doesn't go the way you expected, this is all part of a longer journey and a learning experience in itself. Enjoy this time; there will be meetings that make you feel excited. Thank people who have kindly given you their time to give you research advice, but remember you don't always have to take it. What you want from a research project is unique as you are.

Find a great person to work with: Find yourself someone who inspires you and someone you get on with. Ask their group

members what it's like to work with them, look at their track record of success: What journals do they publish in? How many of their PhD students completed their degrees? Are they accessible? How do they run their group meetings? Is this a place where you can talk, think and grow scientifically? Take your time to make decisions about supervisors and projects. Two or three years is a long time.

Try it out: If time and funding permits, try a project out for a month or more to see whether you like it and whether you are good at it. Not everyone enjoys lab work or learning to program; the best way to find out is to try it.

Know your strengths and your weaknesses: Know yourself and play to the things you excel at, and minimise exposure to your weaker areas. Also try to understand what the project entails and how it will fit into your life. Some projects, for example cell work, might involve lab work at weekends. Could you commit to this?

Bring clinical knowledge and skills: As a clinician you are behind your scientific colleagues in terms of exposure to science. What you can bring to the arena though is a wealth of clinical knowledge, skills and experience, and the value of this should not be underestimated.

Learn to program: In these days where genomic data are flooding in, learning a computer programming language (such as UNIX, Perl, Python or R) is an excellent skill for Clinical Geneticists to have. If learning to program makes sense with your PhD project then do so! Being able to write your own programs gives you the freedom to interrogate data in exactly the

way you want to. Even if you don't continue to write programs yourself post your PhD, these skills will stand you in excellent stead when interacting with bioinformaticians and interpreting the results from genomic testing in the future.

So how do you learn a computer programming language?

1. Do a course to learn the basics
2. Have a mentor who can help you
3. Have a problem to solve
4. Use online help sites
5. Persevere

Develop your resilience: Research can be tough, one of the most vital skills to develop is resilience, work on this. Every legendary scientist I have met or heard talk has been through difficult times and thought about giving up, but something made them keep going. Find your something.

And finally, trying to advance knowledge of humans (even just a little bit) and ultimately help patients is an immense privilege, good luck. But remember, all of this is just my advice, and of course, you don't have to take it.

Apps for genetics

Mary O'Driscoll, Birmingham



TGCA

It used to be that the most interesting thing in my clinic kit, and only for small children, was a retractable

measuring tape with ladybirds on. It seems that I may have found something that might keep the whole family involved. TGCA (The Genetic Counselling App) is a tablet-based visual aid for genetic counselling in the clinic environment and a new alternative to the increasingly battered folder of useful images I have carried to clinic for the last few years. Thanks to the technically talented folks at St Georges, TGCA is a paid genetics app for us technically-challenged neophiles. Tablet technology is ubiquitous. If you don't have one to hand ask your nearest medical student and download the app for iPad.

What does it provide? Animations based on three common areas covered in a genetics consultation; mendelian inheritance, common genetic tests (including arrays) and chromosomes. Navigating the options available is straightforward with different speeds for the animations, a pause button and a choice of colours for the inherited chromosome. I wasn't immediately sure of the reason for the latter until, having decided to try it out in clinic, I got one of my younger patients to join in and choose the variables. An immediate hit. It was popular with teenagers too and is certainly a suggestion for those young people who are more reluctant to engage in conversation. Clearly, using an app cannot replace the face to face aspect of an appointment, but like our printed copies acts as a useful adjunct. Using animations rather than static images certainly made me re-adjust my usual clinic patter.

The app links directly to other resources including Unique and GeneReviews. This I can envisage being useful for non-genetics specialists too in the management of common genetic disorders, particularly

where they link to management or diagnostic guidelines. Unfortunately this capacity is limited by access to internet and, for me, universal wifi coverage can't come quickly enough.

What else is out there? There are a few other apps to tempt.



GROWTH CHARTS UK-WHO (free)

Smart and simple phone app from the paediatricians behind the paediatrics.co.uk

website. Based on the up to date WHO growth chart data, input the date of birth, measurements, gender and gestation for an instant centile calculation. Not so useful for those whose growth falls outside the normal parameters however, so don't get rid of your paper copies yet.



PROBAND (paid)

Clear and intuitive pedigree drawing software app for iPad with built-in HPO data, quick data input and free text

panel. The lack of individual identifiers (name and date of birth) keeps it anonymous. Useful both in whipping up a quick and tidy family tree to annotate later or to add polish to a presentation.



ORPHANET (free)

Who wouldn't love the orphanet app? Available for phone and iPad it's useful on the go and in clinic to look up the occasional surprise in the patient's family. Some functions such as diagnostic test information require wifi/3G to access.



3D-BRAIN (free/paid)

An interactive, annotated 3D brain image app. Consider this if you ever have to explain

brain involvement in your favourite syndrome. The free version looks great or upgrade to a paid version available for those of us with a cerebral obsession.



BIOGENE (free)

A phone based search app for gene information from Entrez Gene at NCBI providing referenced

information on gene function. Requires wifi/3G to access much of the information.

CGS News Editor



Deadline for contributions for next issue is 30 April 2015

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CGS International Scholarship

Dr Neerja Gupta (MD, DM Medical Genetics)
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I can still remember that late October 2012 evening, when I received a letter from Dr Elisabeth Rosser, informing that I have been awarded the UK Clinical Genetics Society (CGS) International Scholarship. I was delighted at the thought of being able to have a firsthand experience of clinical genetics work in the UK. Dr Rob Elles was instrumental in finalising a schedule that would help me make the most out of my trip. I chose Manchester as my visit centre since it was the place where exciting work was being done in the fields of dysmorphology and metabolic disorders; my areas of interest. During my visit to St Mary's hospital at Manchester, I met several renowned dysmorphologists such as Dian Donnai, Jill Clayton-Smith, Brownyn Kerr and several others. I met the Willink metabolic team notably Dr John Walter, Dr Andrew Morris, Dr Simon Jones and Dr Umaramaswami. I was deeply touched by the warmth and hospitality of the entire Clinical Genetics Department of St Mary hospital. I attended their routine prescheduled meetings, their clinics and ward rounds. As I had expected, both the infrastructure and work culture in Clinical genetics at Manchester was amazing.

At Manchester, I noticed several differences in work patterns, of which the notable ones were-

- Apart from having big, spacious, well equipped cytogenetics, molecular, and biochemical genetics labs the major difference that I noted was that each clinical geneticist had identified an area of sub-specialisation and all their energies were concentrated in that particular area.

- The important role played by genetic counsellors was very much evident. Because of their counselling work, the burden on the clinicians is much less and they can therefore focus more into basic and applied research.
- Diagnosis of most dysmorphic syndromes is clinical backed up by the availability of specific genetic tests that further improves the clinical acumen.
- Concept of transition clinics for various inherited metabolic disorders was quite thoughtful and stresses the importance of liaison between metabolic specialists and adult physicians after a particular age.

During the scholarship, I was given the opportunity to present interesting cases at the dysmorphology meeting held in London on 13 March 2013. I also attended the CGS Spring meeting (14 March 2013) in London. Both these meetings were a huge learning experience. I presented my poster entitled *The application of chromosomal microarrays in managing developmental delay in a major genetic centre in India*. The presentation was well appreciated.

To conclude, this scholarship was a great learning experience. It gave me insights for improving the clinical genetics services at our centre in India. For this, I will be always thankful to the CGS. Last but not least it will be my future endeavor to establish long lasting mutually beneficial links between the unit at Manchester and the All India Institute of Medical Sciences, New Delhi, India.

Trainee Column

Hannah Titheradge, Birmingham

Funding

The CGS has several bursaries available to assist trainees in gaining further experience. A complete list can be found on the CGS website at <http://www.clingensoc.org/information-education/trainees/trainee-bursaries/> and are detailed below. These include bursaries for a great opportunity to visit another centre either in the UK or internationally as a short elective period included in our training. Please contact the CGS office via email at cgs@bsgm.org.uk for more details on how to apply.

- | | |
|--|----------|
| 1. Bursary to attend another centre (UK or abroad) | £400 x 3 |
| 2. Bursary to attend BSGM conference | x 2 |
| 3. Bursary for study leave – meeting or work | £400 x 3 |
| 4. Robin Winter SpR Prize | £200 |

Social media

There is now a CGS trainee facebook group at <https://www.facebook.com/groups/GeneticTraineeUK/> kindly set up by Rhoda Akilapa (Sheffield). This is a closed group so approval will be needed. In addition, the Yahoo Genetic SpR group continues, please contact me on the email address below if you would like to join this group. The CGS twitter account @clingensoc is also still going strong.

The future of Clinical Genetics

Thank you to everyone who joined the discussions on Facebook and the Yahoo group about the future of clinical genetics. Thank you also to everyone who completed our survey, kindly put

Obituary – Dr Louise Anne Brueton 1961-2014

Jenny Morton, Birmingham

together by Anna Znaczk (Belfast). It was very interesting to hear everyone's views. It appears that many of us feel we need additional training, particularly in bioinformatics, pharmacogenetics and statistics, to better equip us for this future. There are certainly plans in motion to try to help us bridge this gap and we await further information on this.

Anna, Emily, Verity, Vicky and I represented the trainee views at the recent joint meeting between the CGS council and the Lead Clinicians. We will send out further information about the conclusions of this meeting when the report has been drafted.

CGS Council SpR representatives

There are currently two trainee representatives on the CGS council. I am due to finish my stint on the council at the end of this year, so please watch out for elections at the beginning of 2015! I have been very grateful for the opportunity to sit on the council representing trainees nationally and would strongly urge interested trainees to apply. There is also the possibility to become involved in sub-committees of CGS, which I would also recommend where possible.

Views and Issues

If you have any views that you would like discussed nationally at the CGS council meetings, please contact myself (hlthieradge@doctors.org.uk) or Emily Craft (Emily.craft@uhl-tr.nhs.uk). Training issues should be directed to the SAC representatives, Verity Hartill and Victoria McKay.



Louise was born in Birmingham and attended medical school at the Royal Free Hospital, London. She graduated in 1984 and continued her training in paediatrics at the Queen Elizabeth Hospital for Children, Hackney and St Thomas' Hospital, London. She entered genetics in 1987 with an MRC Fellowship under Bob Williamson at St Mary's Hospital and Robin Winter at the Kennedy Galton Centre and was then appointed as Senior registrar at the Kennedy Galton Centre in 1989. She was awarded her MD thesis entitled *Craniodigital syndromes and Chromosome 7p* in 1996 and was made a fellow of the Royal College of Physicians in 1999. She was appointed as a consultant Clinical Geneticist at the Kennedy Galton Centre in 1993 and then moved to Birmingham, the city of her birth, schooling and marriage, in 2000. It is here that I had the privilege of working with her.

On arriving in Birmingham, Louise wasted no time in reviewing the genetics service for paediatrics in the West Midlands and established regular general genetics clinics and joint neurometabolic clinics at Birmingham Children's Hospital. Louise also contributed nationally to dysmorphology, as a facilitator at the National Dysmorphology meetings at Great Ormond Street Hospital in London and founded the very successful Midlands Dysmorphology Group. Louise worked tirelessly to provide the very best service possible for patients and most recently was instrumental in providing the case for introducing microarray analysis in to routine service in Birmingham. She was also very active in research, always striving to improve knowledge for the good of patients.

Sadly, Louise became ill in 2011 and had to retire due to ill health in 2013. She fought her illness with characteristic courage and humour and continued to be a regular visitor to the department, contributing to clinical meetings and teaching of trainees for as long as she could.

Louise was a dedicated and loyal colleague who was passionate about her work, patients and family. She had great clinical acumen and was always willing to help and advise her colleagues and trainees. She will be greatly missed by her colleagues, patients, family and friends. She is survived by her husband Phil, and sons Greg and Matt.

Louise Anne Brueton: Consultant Clinical Geneticist, Birmingham Women's NHS Foundation Trust and Honorary Senior Lecturer, University of Birmingham.
b. 1961 d. 23 September 2014

Editorial

Welcome to the latest edition of the CGG newsletter. Myself and Helen Hanson have recently taken over as the editors of this section of the BSGM newsletter, we hope you'll find our first edition an interesting read. We'd like to thank Emma Woodward and Andrew Cuthbert, our predecessors, for all their hard work in delivering previous editions.

The lead article is an interesting and thought-provoking piece by Professor Anneke Lucassen on the challenges of consent as we approach the era of genomic testing in a clinical setting. Anneke explores how differences in the language surrounding consent can alter the context in which that consent is taken. Anneke makes the important point that just because a patient has consented to a test or procedure does not mean that they necessarily have the right to access to that test. Issues around consent are relevant to our daily work and this is a timely piece as the challenges of taking meaningful consent are increasing, as the ways in which we are able to offer genetic testing become more sophisticated. Anneke has set-up and is the chair of a BSGM sub-committee that will hopefully be able to provide our community with guidance in this challenging arena.

The article by Ian Frayling on Systematic testing for Lynch syndrome in all patients diagnosed with bowel cancer below the age of 50 years, and potentially beyond that age, is also timely as it comes six months after the death of Stephen Sutton, an exceptional young man diagnosed with bowel cancer at 15 years of age due to Lynch syndrome. Stephen's experience has not only led to a very successful fundraising campaign but has also raised the profile of Lynch syndrome

in the media. Later in the newsletter we have a short piece from Anna Beach, genetic counsellor, on a patient support day organised earlier this year for patients and families with Lynch syndrome.

The Royal College of Pathologists have presented best practice guidelines that suggest that all bowel cancers in patients below the age of 50 years should be tested for the presence of a mutation in a mismatch repair gene. Such a change in practice will undoubtedly have an impact on cancer genetics services all over the country. Whilst this would be a positive move as more families with Lynch syndrome would be identified, it is important that we are mindful of potential conflicts which could arise from this. How will we ensure that patients are aware that they are undergoing a test that could have implications in terms of their own future cancer risks, and which may also have implications for their relatives?

The question above is one that is often asked in relation to mainstreaming in cancer genetics. Daniel Riddell and Professor Nazneen Rahman have provided us with a useful Update on the Mainstreaming Cancer Genetics (MCG) Programme that they are leading at the Institute of Cancer Research, in partnership with the Royal Marsden hospital. Their MCG programme seems to have successfully addressed this question.

Those of you who were at the CGG Winter Meeting in December will have heard Sam Smith from the Wolfson Institute of Preventative Medicine give a presentation on the ENGAGE study. The study aims to explore decision-making in breast cancer chemoprevention. The study also aims to investigate how NICE

guidelines on chemoprevention have been implemented across the country. This is an important new study that many of us could contribute to. Please read Sam's article to find out how you could get involved!

We also have a bit of an international theme to our newsletter this time. We have a contribution from a Trainee Genetic counsellor from Jordan who is currently on a clinical attachment with Julian Adlard in Leeds, Sian Jenkins, trainee Genetic Counsellor reports from the ASHG conference in San Diego, and Kelly Kohut reports on research findings from North America presented by Professor Steven Narod at BSGM in Liverpool in September 2014.

Lastly, Fiona Laloo, chair of CGG gives us a summary of some of the great work that the CGG steering committee and others within the group have undertaken over the past year.

Munaza Ahmed, CGG News Editor

Consent and genetic testing: What is good enough for genomics?

Anneke Lucassen

Professor of Clinical Genetics

Wessex Clinical Genetics Service and CELS unit (Clinical Ethics and Law, Southampton)

What does consent mean in the context of genome analysis? What are the important elements of consent in the age of gene panels, whole exomes and genomes? A discussion about the potential risks and benefits of analysing a particular part of the genetic code (because of signs, symptoms or a particular family history of disease) will be different to that about a whole genome analysis, where the range of possible inferences that can be made, and the degrees of certainty of many of them, are much greater. How can we possibly ensure consent in these settings is 'fully informed', and, anyway, what does this mean? These questions are important, and take on a greater significance as we move to mainstream genomics and as our approaches change from targeted to 'trawling' analyses.

The Department of Health states "it is a general legal and ethical principle that valid consent must be obtained before starting treatment or a physical investigation" and NHS choices tells us that "for consent to be valid, it must be voluntary [not due to pressure by staff, friends or family], informed, and the person consenting must have the capacity to make the decision". So if consent is only valid if the implications of [an investigation] are communicated and understood, can consent to genomic testing be valid when the number of possible outcomes and inferences are much greater than can feasibly be discussed up front, let alone fully assimilated and their implications understood?

Providing consent to an investigation or treatment is an important part of a person's right to self-determination. A greater focus on consent over the last few decades also reflects changing attitudes about what is viewed as acceptable practice and a desire to move away from medical paternalism.

There are some clear legal landmarks in this evolution: Thirty years ago, *Sidaway* case¹ established that the information that should be provided to a patient would be determined by the application of the 'Bolam Test'; that is, what a reasonable body of medical opinion would agree would be sufficient for patients to make an informed decision. Aside from the obvious paternalism inherent in this ruling, the problems for such a test in a rapidly developing clinical practice such as genomics are obvious. The *Bolitho*³ case challenged the principle of the Bolam test considering information to be adequate if it is what a reasonable patient might want to know. Lord Woolfe, in *Pearce v United Bristol Healthcare NHS Trust*⁴ ruled that "the reasonable doctor must tell the patient what the reasonable patient would want to know". So, what does the reasonable patient want to know about genomics, and how can a reasonable patient decide at the point of testing what they would or would not want to know? What is the reasonable health professional able to tell a patient about genomics, especially when most outputs are far less deterministic than popular portrayals make them sound?

The other thing we need to remember is that the consent process is not a mechanism for enabling a patient to choose whatever investigation they want. Whilst patients can, and should be able to, refuse medical treatments they cannot have whatever treatment or investigation they want. Just because a patient wants to be tested for breast cancer genes does not mean that respecting their right to self-determination means we are obliged to provide them with that test. Wanting a test and consenting to it are not the same thing. Consent in this setting has to be more than simple permission giving, particularly because we have evidence from established

predictive genetic testing programmes that a person's initial wishes are often different to their considered decision. It also has to be more than a signature on a form. Documentation of discussions in a patient's notes may sometimes provide better evidence of consent than a signature on a form. As Grubb⁵ also points out "valid legal consent is given even where the patient does not demonstrate [her] agreement providing that *the state of mind* was, in fact, that [s]he agreed. In other words, an unexpressed actual consent in law is a valid consent"

Our job as health professionals is to try and ensure our patients' choices are as informed as possible and this may mean highlighting some difficult issues. This is particularly so for the vexed topic of 'incidental findings' in genomics. The reactions to the ACMG guidance earlier this year were very focussed on giving patients the right to say 'no' to certain findings, and less on whether it is really possible to provide consent and refusal to a range of possible unknown findings. Patients should, of course, be able to say 'no' to certain things, but this 'no' should be an informed one and therefore the consent process needs to be more than a tick box exercise. This also means that if a health professional is not convinced the refusal was sufficiently informed, and harm is more likely to be prevented by disclosure (through availability of surveillance or other interventions) then such refusal does not have to be observed at all costs.

Confusion about what consent should look like in medical practice more widely is in part reflected by the number of qualifiers or adjectives we place in front of the word: 'Informed consent'; 'fully informed consent', 'sufficient' and 'real' are all to some extent tautologies since they are also part of the definition of consent itself: surely consent is

Systematic testing for Lynch syndrome

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

not really consent unless it is informed? Then, there are adjectives like specific, generic, open ended, broad, presumed or implied which might be placed before the word consent in an attempt to nuance the nature of consent. If health professionals can be well enough attuned and responsive to different situations and different levels of understanding, then perhaps, like Winnicott's good enough parenting, we should be striving for good enough consent.

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3. Bolitho v Hackney Health Authority (1998) AC 232, (1997) 4 All ER 771, HL, (1998) 39 BMLR 1
4. Pearce v United Bristol Healthcare NHS Trust (1999) PIQR 53; (1998) 48 BMLR 118
5. A. Grubb, Consent to treatment, the competent patient. Principles of medical law, I Kennedy and A Grubb (eds) OUP (1998)

Earlier this summer "A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome" was published, shortly after a similar piece of work in The Netherlands.^{1,2} The NHS health technology assessment, which runs to 448 pages with the 16 appendices, indicates that it would, according to the NICE reference case, be cost-effective for the NHS to implement systematic testing of colorectal cancers for Lynch syndrome. In other words, the cost of finding new cases of Lynch would be less than the maximum of £20,000 per Quality Adjusted Life Year (QALY) gained, the level at which new therapies and technologies are judged worthwhile to implement (in The Netherlands their limit is €80,000 or ~£65,000).

The study looked at six different testing strategies (combinations of MSI, immunohistochemistry and *BRAF/MLH1* methylation), compared with doing nothing. It also looked at simply testing incident cases of bowel cancer for mutations in the four mismatch repair genes (*MSH2*, *MLH1*, *MSH6* and *PMS2*) – although doing this in reality would not be the current way of doing things, we could model this in *silico* to see how it compares.

The results based on testing all cancers up to age 50 show that of all the tumour testing-based strategies considered, MSI, followed by *BRAF*, and then referral to clinical genetics was the most cost-effective at £5,500 per QALY, whereas simply 'sequencing' everyone would cost £83,000/QALY. However, all strategies based on tumour testing came in well below £10,000/QALY. Increasing the age cutoff to 60 years, would cost £7,700/QALY for MSI/*BRAF*, and even up to age 70 years it would still be only £10,800, well below the £20k threshold.

So, one way of looking at this is that if it was a new cancer drug there would be an excellent case for its introduction. The Netherlands work shows similarly that it would be cost-effective for them to increase the age at which testing is done to age 70, however, the yield of Lynch drops off considerably over this age and for a given amount of resources it would probably be better to test incident cases of endometrial cancer, women who have had both colorectal and endometrial at any age, and other rare Lynch-associated tumours, such as small bowel and hepatobiliary cancers.

It was also determined that whilst the cost-effectiveness was improved by extending genetic testing to relatives, it was actually cost-effective merely to find index cases, because of the different treatment they would then receive reducing their risks of metachronous cancers.

In countries such as Denmark in which this is already being undertaken the results are encouraging. There they do not have an upper age cutoff and recent data presented at the 7th European Multidisciplinary Colorectal Cancer Conference shows ~3.2% of all colorectal cancers are due to Lynch, with approximately equal numbers of cases attributable to each of the four genes, unlike the experience of genetics clinics where case referral is biased towards early onset and complete penetrance.

In July this year the Royal College of Pathologists Minimum Dataset for Colorectal Cancer (aka best practice guidelines) was updated, with the SAC having sight of the NHS health economic analysis, and now states that testing of all colorectal cancers in the UK up to age 50 for deficient mismatch repair must be

"according to NICE (it would) be cost-effective for the NHS to implement systematic testing of colorectal cancers for Lynch syndrome"

carried out.³ It acknowledges that the case for testing all cases up to age 70 is established (in part also because of the prognostic and predictive value), but that until funding is identified by commissioners it cannot be demanded.

On the basis of this, and coinciding with it being six months since the death of Stephen Sutton at age 15 from bowel cancer due to Lynch syndrome, Bowel Cancer UK has launched a "Never too young" campaign including systematic testing for Lynch, as a part of which many colleagues have given their support in an open letter to *The Daily Telegraph*. Bowel Cancer UK hope that all services will soon comply with the RCPATH minimum dataset and an age cutoff of 50 years, together with sufficient provision of colonoscopic surveillance, following which the age cutoff will rise to 70. However, for that to happen it will ideally require a co-ordinated approach to implementation across the four NHSs of the UK, and some central funding to start it off, bearing in mind that the ultimate aim is to prevent as many expensive and life-shortening cancers as possible.

It has to be borne in mind however, that we were only able to consider the ability of colonoscopy and hysterectomy/oophorectomy as life-saving procedures, and also that the costs of testing are constantly coming down. Allied to this, aspirin prophylaxis promises to reduce mortality from all Lynch cancers and vaccines against MSI tumours may well be on the way. So, the cost-effectiveness of finding cases of Lynch can only increase.

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Update on the Mainstreaming Cancer Genetics programme

Daniel Riddell, Programme Manager, Mainstreaming Cancer Genetics and Professor Nazneen Rahman, Head of Cancer Genetics, The Royal Marsden NHS Foundation Trust, Head of the Division of Genetics and Epidemiology, The Institute of Cancer Research

The Mainstreaming Cancer Genetics (MCG) Programme is a cross-disciplinary, translational initiative to develop the assays, informatics, clinical infrastructure, education, ethics and evaluation that will allow implementation of (germline) cancer genetic testing into the routine clinical care of cancer patients and their relatives. The programme is led by The Institute of Cancer Research (ICR) in partnership with The Royal Marsden and funded by the Wellcome Trust. The programme will run until 2016.

A key aspiration of the programme is to develop clinical pathways which allow more people with cancer, and their families, to benefit from cancer predisposition gene (CPG) testing.

Towards this objective, we have developed a 'mainstream' gene testing pathway, which gives people with cancer the option of having CPG testing through their routine oncology appointments. In this model, CPG tests are carried out by members of the cancer team who have completed an online training course developed by the programme. Anyone in whom the CPG test shows a pathogenic mutation automatically has an appointment with genetics, so that the implications for themselves and their families can be discussed further. Those without pathogenic mutations can also have appointments with genetics should they wish to.

We have now fully implemented mainstream BRCA gene testing for women with breast and ovarian cancer at The Royal Marsden.

Over 250 people have now received BRCA tests through the mainstream pathway. A survey of women with ovarian

cancer who received BRCA tests through this pathway showed that:

- 100% (77/77) were happy they had the test
- 99% (76/77) were happy to have the test through oncology

Every woman with ovarian cancer offered a BRCA test chose to have testing. 17% of women with ovarian cancer tested were found to have a BRCA mutation. The results of the pilot phase of this implementation are currently being written up for publication in early 2015.

The mainstream gene testing pathway has now been adopted as standard practice by the breast and gynae units of The Royal Marsden; all women with non-mucinous ovarian cancer, and all women diagnosed bilateral breast cancer <50yrs, Triple-negative breast cancer <50yrs or breast and ovarian cancer at any age are now routinely offered BRCA testing via oncology as a standard part of their care.

We are now investigating how to further increase access to gene testing for other genes and other cancers. In particular we are planning to make the mainstream BRCA testing criteria for breast cancer at The Royal Marsden more permissive, so that many more people can benefit.

The programme has made the full mainstream pathway and training materials available through the programme website (www.mcgprogramme.com/brcatesting) so that other units can make use of them.

The work being carried out on the programme was highlighted by Paul Burstow, MP for Sutton & Cheam, during

a Westminster Hall Debate on 4 November 2014. Mr Burstow told the debate that the programme "shows that productivity is increased by doing the testing as part of an oncology appointment, rather than as something separate. The trials are delivering that in a way that is not costing the NHS more, and it is having huge benefits."

Decision-making in breast cancer chemoprevention: The ENGAGE study

Dr Sam Smith, Cancer Research UK Postdoctoral Fellow, Centre for Cancer Prevention, Queen Mary University of London, Wolfson Institute of Preventive Medicine

Following the publication of the NICE familial breast cancer guidelines in 2013, a new option for breast cancer risk reduction became available to women at elevated risk of the disease. This announcement came after the publication of multiple randomised controlled trials which demonstrated a reduction in breast cancer incidence among women taking Selective Oestrogen Receptor Modulators (SERMs). The magnitude of the risk reduction from SERMs was estimated to be 38% in a subsequent meta-analysis.¹ The NICE guidance outlined that healthcare professionals within specialist genetics clinics should offer one of two SERMs, Tamoxifen or Raloxifene, to women at high risk of breast cancer, and consideration should be given to making these medications available to women at moderate risk.

Chemoprevention is undoubtedly a useful addition to the options available to women at elevated risk of breast cancer. However, at a time when patients are already engaging with unfamiliar information, the decision to take chemoprevention may be burdensome. In addition to the standard counselling available during consultations, patients will be asked to process information about the risks and benefits of chemoprevention, and make a decision that fits with their personal preferences. For the majority of patients who are unfamiliar with even basic health information, the decision to take chemoprevention will be a difficult one. Furthermore, we all carry our own preconceptions about health and illness, and our tolerance of risks and benefit varies widely. To what extent will these psychological factors contribute to patient's thoughts about chemoprevention and its use?

In an interdisciplinary collaboration funded by Cancer Research UK, the ENGAGE study was formed to investigate questions such as these. Using a mixture of one-to-one interviews and surveys with patients and clinicians, the ENGAGE study will investigate how breast cancer chemoprevention is being implemented across the UK. Over the next six months we are recruiting clinicians to take part in a brief interview study investigating how the NICE guidelines have been interpreted in local settings. If you would like to help us with this research, please email Dr Sam Smith (sam.smith@qmul.ac.uk). We would also like to hear from you if your clinic is interested in assisting with recruitment for a planned patient survey. Starting in May, 2015 we are aiming to approach approximately 3000 women who are at increased risk of breast cancer to give us their perspective on chemoprevention. Baseline recruitment will be open for one year, with planned follow-ups at two months and one year. As a Cancer Research UK funded study, the ENGAGE study is eligible for National Institute for Health Research (NIHR) portfolio funding to support centres that are able to help. With your help, we hope to gain an insight into how chemoprevention can be integrated into clinical care, and how women can be best supported during the decision-making process.

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A Jordanian trainee's perspective on cancer genetics services

Lama Abujamous, Trainee Genetic Counsellor supervised by Julian Adlard, Consultant Clinical Geneticist, Leeds

Five and a half billion of the world's 7.1 billion population live in developing countries. Most of these people do not have access to services that could provide genetic counselling and diagnostic tests for familial cancer risk. It is expected that, over time, services currently available in developed countries will become increasingly available elsewhere.

King Hussein Cancer Center (KHCC) in Jordan is one of the most specialised centres in the Middle East dedicated to the treatment of paediatric and adult cancer patients. KHCC was established in 1997, as a non-governmental, not-for-profit comprehensive cancer care organisation. KHCC currently treats more than 3500 new patients per year, and in 2015 a new expansion is due to open which will increase the capacity to about 9000 new cases per year. Limited germline cancer genetic testing is currently available from an external provider in specific circumstances. However, there is no comprehensive cancer genetics counselling or testing service. We have a molecular diagnostic and immunogenetics laboratory. This provides a range of testing, but not currently germline DNA analysis.

The KHCC vision and strategic plan includes improving access to education, training, and research in collaboration with international centres. We will aim to set up a cancer genetic counselling and testing service. As breast cancer is the most common genetic cancer, we may start with this type of cancer, and then expand to other cancers with a familial tendency and known predisposing genes. Within KHCC there are sub-specialised services for different sites of cancer, managed by oncologists, surgeons and

other specialists. In the future, we will aim to provide genetic counselling support for these services and enable access to genetic testing in line with international standards.

In relation to the educational and training programme, I have begun a six month clinical attachment in the Yorkshire Regional Genetics Service based in Leeds, under the supervision of Dr Julian Adlard and his team. My background is in laboratory science including a Master's degree in molecular biology and human genetics. The aim of the attachment is to obtain experience of cancer genetic counselling as practised in the UK. This includes gaining understanding of risk assessment methods, availability of genetic testing, screening or preventive options, and discussion with patients and their other responsible health professionals. We should be aware of psychological and emotional issues, and potential consequences of the test results. Confidentiality of genetic information is very important.

I have gained experience in these aspects through attending clinics and other activities with different members of the team. I have also spent time in the Regional Genetics Laboratory observing the available testing, including advanced techniques such as Next Generation Sequencing and Capture Array cancer panel testing, along with analysis methods and reporting.

KHCC has focussed on treatment of patients already affected with cancer, whereas I have learned that much more of the work in Cancer Genetics is directed at assessing risk in unaffected family members. This would lead to a change in types of patient seen and we will consider

referral pathways for unaffected at-risk patients to KHCC.

The future level of demand in Jordan is not yet certain, but it is likely to increase as more members of the public become aware. Also, medical staff at KHCC already recognise hereditary issues and wish to refer patients for assessment and possible genetic testing. There are challenges to introducing wider germline genetic testing, but we will aim to develop a Next Generation Service for genetic testing 'in house' in the near future. I am looking forward to working with colleagues to develop this further in Jordan when I complete my attachment.

The ASHG meeting in San Diego: A Trainee Genetic Counsellor Experience

Sian Jenkins, Trainee Genetic Counsellor, Wessex Clinical Genetics Service

In October this year I attended the 64th Annual American Society of Human Genetics meeting in San Diego. The conference held over 5 days was attended by over 8000 delegates and was packed with exhibitions, poster presentations, invited speakers and interactive activities. The conference was a great opportunity for me to learn about the exciting developments currently being made in the field of cancer genetics, and to network with our overseas colleagues.

The topics for concurrent speaker sessions were vast and covered most aspects of genetics. From neuropsychiatric disorders to circadian disorders, the genetics of obesity to reproductive genetics, it was difficult to make the most of the expertise on offer and some careful timetabling was needed to make the most of the experience.

A focus on cancer genetics was evident in the programming, with a session based in cancer genetics in almost all of the seven concurrent platform sessions. These sessions varied from a focus on genomic alterations of tumours to cancer type specific topics such as hereditary breast and ovarian cancer. The conference also had almost 300 poster presentations based in the field of cancer genetics, making it one of the most represented fields within the conference.

A significant emphasis on the use of whole exome or whole genome and its clinical utility for our patients was evident in many of these posters and sessions. With the development of multi-gene panels and its increasing use in clinical genetic testing I was interested to hear about the experiences and challenges others have had.

One study from the University of Washington, presented the benefits and challenges of using multi-gene panels by reporting their study into two multi-gene panels, one containing 19 genes, the other containing 51 genes. Although the 51 gene panel identified actionable mutations in 10% of patients who had already had BRCA1 and BRCA2 testing and 13% of patients with pathogenic or likely pathogenic variants, it also identified 10% with variants of uncertain significance. Similar figures were also produced by the 19 gene panel with 13% of patients carrying variants of uncertain significance. The increasing frequency in which this type of genetic testing is taking place in genetics here in the UK is likely to continue providing us with some uncertain and tricky information to interpret on behalf of our patients.

I was also interested to hear the comparison of genetic testing criteria in the United States to here in the United Kingdom. In particular, one speaker presented their figures on the number of females with triple negative breast cancer related to BRCA1 and BRCA2 gene mutations. American guidelines recommend testing all individuals with triple negative breast cancers under the age of 60, an additional twenty years on the age criteria provided by the NICE guidelines. The speaker explained that their study found that 24% of triple negative breast cancers over the age of 40, in the absence of a family history, have a BRCA gene mutation, suggesting the need for an increase in the age threshold required for BRCA1/2 testing here in the UK.

The conference was a great experience as a trainee genetic counsellor and left me with lots of food for thought as well as new friends across the pond.

BSGM Annual Conference: Symposium by Dr Steven Narod on the management of hereditary breast cancer

Kelly Kohut, Genetic Counsellor, Royal Marsden Hospital

Dr Steven Narod is Director of the Familial Breast Cancer Research Unit at Women's College Research Institute in Toronto. He presented at the BSGM conference in Liverpool in September 2014 on his research involving women with hereditary breast cancer. We attended his talk with interest as many of his findings have impact for clinical practice and we were interested to see how practice varies in Canada compared to the UK. The main topics he discussed are outlined below.

Predictors of contralateral breast cancer risk

Dr Narod commented that in Canada 24% of women with breast cancer (regardless of genetic status) are choosing to have bilateral mastectomy, and this was due to patient choice rather than surgical recommendation. In the UK, NICE recommend that rapid genetic testing at diagnosis should only be performed as part of a research study, but breast teams are increasingly requesting testing to aid management decisions.

In a study of 810 women with stage 1-2 breast cancer and a *BRCA1* or *BRCA2* mutation, the risk of contralateral breast cancer was 42% for women under age 40.¹ Younger age at onset and family history of breast cancer increased the risk of contralateral cancer, and tamoxifen or bilateral salpingo-oophorectomy (BSO) decreased the risk. In 20 years of follow-up, 60% had a new event (recurrence or new primary in the ipsilateral or contralateral breast) while 40% of women who chose ipsilateral mastectomy still had a new event. Dr Narod concluded there was not a strong rationale for choosing ipsilateral mastectomy at time of diagnosis because the main benefit came from preventing contralateral breast cancer.

While survival benefit for bilateral mastectomy has not been found in the general population,² the optimal treatment for *BRCA* carriers seems to be bilateral mastectomy at diagnosis, which prevents local recurrence, contralateral breast cancer and improves survival. In women with stage 1-2 breast cancer and a *BRCA1/BRCA2* mutation, most fatal cancers between years 15 to 20 of follow-up were from contralateral breast cancer.³ In the UK, we counsel carriers about the option of bilateral mastectomy but the decision is ultimately patient choice. More information about survival benefit may influence decision-making about risk-reducing surgery in future.

Impact of BSO on mortality

In addition to preventing ovarian cancer, BSO reduces the risk of all cause mortality, which included a benefit from reducing breast cancer recurrence, death and second primary breast cancer.⁴ BSO seems to be particularly effective in reducing death in *BRCA1* mutation carriers with oestrogen receptor negative breast cancers (up to 70%), but this requires further study. Dr Narod's group looked at women who chose not to have BSO because they wanted to have a child after breast cancer treatment. Pregnancy did not impact survival, but BSO significantly increased survival.⁵

A 4% risk of ovarian cancer was reported if *BRCA1* mutation carriers waited until age 40 to have BSO, while the risk before age 35 was only 1%.⁴ This supported the recommendation in North America to consider BSO by age 35, which differs from The Royal Marsden recommendation to consider from age 40. In our patient population, many women have not had children yet and therefore desire for children needs to be balanced with the low

risk of ovarian cancer below 40 years. In 2013, over half (51%) of all UK live births were to mothers aged 30 and over and the average age of all mothers increased to 30.0 years (www.ons.gov.uk). Therefore it is important to take into consideration both side effects of an early menopause and reproductive decisions and provide patients with appropriate information.

Should all *BRCA1* mutation carriers receive chemotherapy?

The survival of 455 *BRCA1* mutation carriers with node negative, 0-2cm grade 1 breast cancer was much poorer than expected.⁶ The survival in those who had chemotherapy was 90% compared to 75% in those who did not have chemotherapy. The addition of chemotherapy increased the survival rates compared to non-carriers with similar grade 1 cancer. Dr Narod concluded that all *BRCA1* mutation carriers with breast cancer (even those with a good prognosis cancer) should have chemotherapy, and we need more information on platinum-based chemotherapy.

In a trial in Poland of *BRCA1*-associated stage 1-3 breast cancer treated with neo-adjuvant cisplatin, 61% had complete pathologic response.⁷ This compared to a much lower rate of 20% or less in women treated with standard regimes. It is thought that there may be a similar effect in triple negative or basal type breast cancer. Dr Narod's group are planning further study in Mexico where the mutation frequency is high.⁸

In the UK, it is not yet standard practice to give cisplatin with small, node negative breast cancer, although this approach is starting to be used at some centres, mainly in the context of clinical trials. More data is awaited from the San Antonio Breast

Cancer Symposium. These potential treatment planning implications make it more important to identify BRCA carriers early on in breast cancer management.

Other genes

Dr Narod plans to create a new study of *PALB2* mutation carriers with breast cancer to examine survival, risk of contralateral breast cancer and whether there is an indication for risk-reducing BSO.

Conclusion

This symposium provided useful considerations for clinical practice. Better data on survival benefit may influence counselling about risk-reducing mastectomy in future. BSO could be considered at age 35, depending on the priorities of the individual. Cisplatin chemotherapy may become treatment of choice in *BRCA1* carriers with breast cancer, even those with small node negative disease. Although we have known about the *BRCA1* and *BRCA2* genes for 20 years, there is still much more to learn. Further research will help to guide management recommendations in the UK.

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Lynch syndrome support morning

Anna Beach, Genetic Counsellor, Wessex Clinical Genetics Service

For six years the Wessex Clinical Genetics Service has held an annual support morning for BRCA mutation carriers. The aim is to provide patients with the opportunity to meet one another and share their experiences. Such days also allow us as a department to make contact with mutation carriers annually to provide updated relevant information. Feedback from these days has always been very positive. We therefore decided to provide the same opportunity for carriers of mutations in mismatch repair genes.

The first, and unexpected challenge, came in naming the morning; 'Lynch or HNPCC'? 'carrier'? We decided on the title of 'the Wessex Hereditary Colon Cancer Information and Support Morning'.

In total 60 people came. Some of the attendees hadn't been seen in a genetics clinic for a long time so it seemed important to re-cap the basics and give an overview of the condition and screening recommendations. This proved essential as during Dr Ahmed's talk there was a great deal of interaction and questions, all very encouraging for the small group discussions planned for later. We also invited, Sir John Burn to come and talk about CAPP3. Again, this prompted lots of discussion within the group.

We had sorted attendees into groups prior to the day. Each group had a member of the clinical team there to facilitate and answer questions. A mid-morning coffee break provided further opportunity for patients to talk to each other in a less formal setting.

This patient support morning was really interesting and provided a really valuable

CGG Chair's Report

Fiona Laloo, CGG Chair and Consultant Cancer Geneticist, Department of Genetic Medicine, Manchester

insight into the challenges faced by this group of patients. It gave attendees the chance to discuss with each other what and how they told their children about the condition, to what extent Lynch syndrome affects their lives and their family stories. It was a privilege to be part of and hear the discussions. Whilst the subject matter was serious and often sad, the atmosphere of the day was generally upbeat and supportive. Feedback from the attendees was constructive and positive. Many wanted copies of the slides from the talks.

Due to the success of the morning we plan to hold another event next year. I would be very interested to hear about similar events that other Genetics Services provide. We found the day a rewarding experience which seems to have met a need from our patients which cannot be offered in a hospital clinic setting.

2014 has been a busy year for all of us – the year started with the excellent meeting in Leiden for which we thank our hosts. It was a great opportunity to meet up with our Dutch colleagues, hear some fantastic talks and see a little of a beautiful city.

Jointly with CGS we undertook a survey of the clinical genetics trainees this year, to try to establish what the long-term aspirations of those currently training in genetics are. We had a good response rate of 83% with 58 respondents. Disappointingly, only 12% of respondents were members of CGG, as opposed to 78% being members of CGS. Given that about 50% of the workload of a regional genetics service is cancer genetics, we were surprised by this. About half the trainees had a background in adult medicine and half in paediatrics, with about 30% of those in training already having a higher degree and 50% or the remaining cohort hoping to gain one during their training. Whilst the majority of trainees had training in specific subspecialties led by a consultant with a specific interest in that subspecialty, 50% of them want a general adult/paediatric case mix as a consultant with a further 20% wanting a mixed adult-only case load. This may be related to the lack of a desire to move: the vast majority of trainees wish for a consultant post either in the centre in which they are training, or in the same geographical region. This strikes me as a little unrealistic and makes me wonder whether, as a profession, we are discussing long-term prospects appropriately at entry into the training schemes. There was only one trainee who wished to subspecialise in cancer genetics and it is therefore important that we in CGG consider how to encourage more trainees into this branch of clinical genetics.

Nationally, there is a huge amount of change on the horizon with the tenders for 100,000 genome project just in and the NHS laboratory re-designation looming. At the same time, we are continuing to run services whilst ensuring cost efficiencies – no mean task. The NICE guidelines on familial breast cancer that were published in June 2013 have resulted in discrepancies around access to genetic testing for BRCA1/2 across the country, with some centres being in a position to implement testing at the 10% level, and others lacking capacity or funding. NICE guidelines are just that – guidelines with no associated requirement for funding. Members of CGG were involved in a UKGTN workshop to establish testing criteria, which also clearly discusses the need for testing individuals with ovarian cancer. As a member of the medical genetics CRG, I have had input into an NHS policy document putting forward the case for funding testing at the 10% threshold. The process around funding in the NHS has proved to be enlightening, but has also emphasised the current economic difficulties facing the NHS as a whole. We await the decision of the commissioners.

Other members of CGG have been busy: there has been a response to a somewhat misleading advert by Myriad genetics in the BMJ; support for the HTA report on widespread testing of colorectal cancers by IHC for MMR proteins and membership of working parties for national guidelines for childhood endocrine tumours. We are also leading the national audit on management of Lynch syndrome.

So, 2014 has been a busy one! 2015 looks the same, although the national landscape this time next year should be

clearer. CGG will continue to be involved in national policies as well as continuing with the remit of research. The spring meeting will be in Manchester and will be a joint meeting with the 14th IMPACH (International Meeting on the Psychosocial Aspects of Hereditary Cancer). We hope to see you there.

CGG News Editor



Deadline for contributions for next issue is 30 April 2015

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