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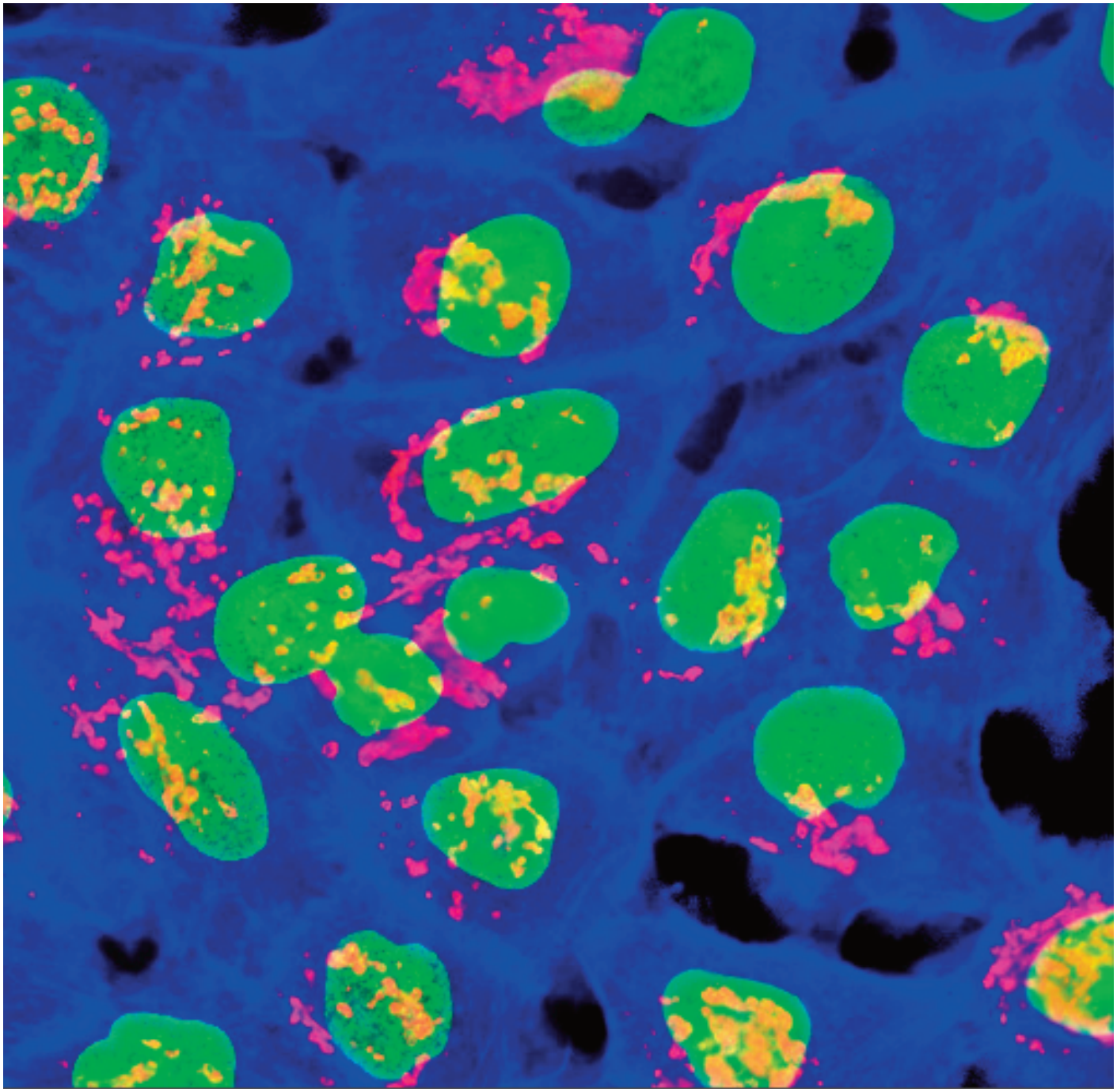
BSGM News



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

From the newsletter editor

Welcome to this very first issue of BSGM News (or the 49th issue of BSHG News). In this issue we are very fortunate to have a number of quality articles describing some exciting developments in genetics and genomics.

Our lead article is from Hanns Lochmüller and Rachel Thompson at Newcastle University. Their overview of the new international initiatives in rare disease research certainly provides an encouraging picture for the future. This is followed by an article from Alain Li Wan Po who summarises a meeting held by the NHS National Genetics Education and Development Centre on the current, and very exciting, state of play in translational genomics.

Each issue of this newsletter is reliant on not only contributions from our members, but also the behind the scenes work by the Editorial Board and Section Editors. This has been even more so for this issue. By the time you will be reading this, I will be on maternity leave. I would like to take this opportunity to thank the BSGM Editorial Board and Section Editors for all their hard work in helping get this issue out, in particular Ann Kershaw who has taken on the finally proofing role for this issue.

I should be back on board for the next issue, so please get in touch if you have any ideas for future articles or features. My contact details can be found at the end of the main section.

Michelle Bishop

From the Chair

John Burn Chair, BSGM

The American College of Genetics and Genomics, which represents the clinical genetics community in the USA, has supported a major policy shift by recommending that anyone having whole genome sequencing should be required to give consent to receive information on any of the major actionable autosomal dominant disorders, regardless of age. The Public Health Genomics Foundation has produced a robust response and the European Society is likely to follow. The British Society for Genetic Medicine must also express its opinion but there is no need for undue haste. The decision of our colleagues in the States is driven by the very different demands of their healthcare system. In the UK we have the benefit of a system which allows a more measured management of such powerful data. The avoidance of discovery in childhood of pathologic variants which will not influence healthcare until adulthood remains an important principle as does the right to be investigated for the condition in question without being faced by an array of often poorly understood genetic changes. Perhaps not surprisingly, the US guidelines make no reference to the reporting of recessive gene carrier status which is defensible on the grounds that future preconception and prenatal decisions will be influenced.

This debate is part of the major changes in our practice which will be forced by the rapid emergence of low cost large scale sequencing. The announcement of the hundred thousand genome project, 100KG to its friends, will place the BSGM and its members at the centre of this global debate. It will be, at times uncomfortable but we must accept the challenge. The next decade will decide whether the practitioners of genetic medicine are integrated with our existing professional groups or practice has become dispersed to the extent that regional genetics centres are marginalised. Similarly, we must come up with ways of managing this powerful information in such a way that it does more good than harm.

Meanwhile, on a lighter note, the new look society will gather for the first time in Liverpool to take advantage of the excellent conference centre. The new Association for Clinical Genetic Science, bringing together the ACC and CMGS, will be officially launched on Merseyside's unsuspecting bars and hostelries. Speaking of getting a skinful, a new group bringing together those interested in genetics and dermatology will be introduced to our ranks under the initial chairmanship of the redoubtable Irwin McLean of Dundee. The group has yet to decide its name. Suggestions are welcome; skinny genes has already been considered and declined.

Rare diseases need global solutions: new international initiatives in rare disease omics research

Hanns Lochmüller, Professor of Experimental Myology, Newcastle University; Chair of the Interdisciplinary Scientific Committee of the IRDiRC; Coordinator of RD-Connect.
Rachel Thompson, Communications and Data Platform Manager, RD-Connect, Newcastle University

Whilst individually uncommon, collectively rare diseases affect as many as one person in every 13 or 8% of the UK population. They span all areas of medicine resulting in a substantial impact on public health, society and economics.

80% of rare diseases have a genetic component, and the advent of next generation DNA sequencing has brought genomics closer to the clinic and raised the expectation of molecular therapies for many rare diseases. Yet the rarity and heterogeneity of these conditions pose specific challenges for healthcare provision and research as well as for the development and marketing of treatments. Many patients with rare diseases still lack timely and accurate diagnosis and even fewer receive tailored therapies that influence survival and quality of life.

Major research funders team up

In recent years, recognition of the specific bottlenecks that research in the rare disease field faces has led major medical research funders to come together in a global grouping that aims to foster international collaboration in rare disease research. The International Rare Diseases Research Consortium (IRDiRC) was launched in 2011 and now has 32 members from across the world, including the European Commission as well as key national funders such as the US National Institutes of Health (NIH) and the UK National Institute for Health Research (NIHR). Each of these funders has pledged to spend a minimum of US$10 million on rare disease research over the coming five years under the IRDiRC umbrella. The IRDiRC has set itself two headline objectives to achieve by the year 2020: to deliver 200 new therapies for rare diseases and develop the means to diagnose most rare diseases. A conference in Dublin in April 2013 under the auspices of the Irish presidency of the EU set the scene for the global research collaborations which this initiative is fostering and provided a strong rallying call for openness and the sharing of research results.

In a world of big data and small cohorts, data sharing is key

With the new technologies that are now becoming available for omics research, there has been an explosion in the amount of research data being produced across the world. This has huge potential not only for gene-finding approaches for the molecular diagnosis of conditions that currently have none, but also in terms of the development of new therapies that address the genetic causes of disease. But the bottleneck in the system is now the analysis of the vast amounts of data being produced by next generation approaches, together with the lack of opportunities to share this data between researchers worldwide. In rare disease, no single centre, and frequently not even a single country has enough patients to be able to do research alone. Every genetics lab has a list of patients who can't be diagnosed because there isn't a second family with a similar phenotype to test. Every pharmaceutical company has made a no-go decision on a potential therapy because simply getting it through the development pipeline was too big a hurdle when individual patients are scattered across the globe and recruiting for a trial would take years.

Yet these problems have potential solutions when a global approach is taken. Resources such as trial-focused patient registries that collect phenotypic data alongside genetic information can dramatically speed up trial recruitment. Research projects across the world are routinely sequencing hundreds if not thousands of patients and results are increasingly coupled to other high throughput readouts such as proteomic or metabolomic investigations. Harnessing this data through advanced systems which enable the comparison of whole exome and genome data across labs and combining it with deep phenotype data and with other omics data types will not only find new genes but also enable better understanding of disease modifiers, biomarkers and therapeutic targets, and accelerate therapy development.

Omics focus

The 2012 funding round of the EU's Seventh Framework Programme saw its largest ever award – a total of €144 million – for rare disease research. Within this sum there was a particular focus on omics research and associated data sharing infrastructure, with €36 million earmarked for this area. Two large omics research projects, EURenOmics (coordinated by F Schaefer, Heidelberg, Germany) and Neuromics (coordinated by O Riess, Tübingen, Germany), focus on cutting edge omics approaches in rare kidney disorders and rare neuromuscular and neurodegenerative disorders respectively, while a large infrastructure project, RD-Connect (coordinated by H Lochmüller, Newcastle), aims to bring together omics data with clinical phenotype data in a central global hub.

This funding came about because there was a recognition of the need not just to harness the power of next generation approaches for the benefit of rare diseases but also to provide a central data sharing system to counteract the 'silo effect' in which research data and results multiply not just in different projects but also in different data types, with inadequate cross-linking. It was important to avoid repeating the current situation, in which it is only too common for there to be no link between, for example, a project on a rare kidney

"Research funders have recognised the issues and are committed to funding international collaboration."

disease in Germany with a project on the very same condition in Spain, but also no link between the sequenced exome of an individual patient with that same patient's clinical data in a patient registry or biomaterial sample in a biobank.

Improved data management, development of unique patient identifiers and advances in bioinformatics tools have the potential to reverse this situation, bringing data together on a large scale so that researchers can compare and learn from results being produced in other centres and even on other diseases. The RD-Connect project is developing an integrated platform in which omics data will be combined with clinical phenotype information and biomaterial availability, accessible online and queryable with a suite of analysis tools. This central hub will make the data generated by IRDiRC projects rapidly available to the wider rare disease research community. Raw genomic data from collaborating projects will be securely deposited in the European Genome Phenome Archive (EGA) before being processed through a standard pipeline to ensure cross compatibility of data from multiple projects. The processed data will be held in the central RD Connect database, where it will be combined with other omics data types plus phenotypic and biomaterial information. Researchers approved by a data access committee will access data through a data coordination centre that enables comparison of datasets across projects and analysis with sophisticated bioinformatics tools.

The success of other large-scale data sharing initiatives in, for example, the cancer field has shown that these approaches can gain traction and benefit the field. RD-Connect is built on the foundations of projects like the International Cancer Genome Consortium (ICGC) and International Human Epigenome Consortium (IHEC). It is also building links with other major variant databases like Decipher in the UK and ClinVar in the US. Despite its roots in EU funding, researchers in the US, Canada, Australia and Japan are integrally involved and committed to sharing data, based on the premise that a central global hub is necessary for maximal utility.

Strong patient advocacy

The rare disease community has a history of strong patient advocacy, with patient advocacy groups like the Genetic Alliance, EURORDIS, the AFM and Fondazione Telethon have been key to raising the profile of rare disease research and making sure that it gets onto the national and international policy agenda. People with rare diseases expect clinicians and researchers working on their conditions to be able to work together. They want to see pragmatic solutions to data protection, coordination and sharing that will enable their data to be used collaboratively for the benefit of research into their conditions. They hope to see their own data used in making progress towards better treatments and better understanding of their conditions and they expect to be partners in that progress. Their support for the principles of data sharing and their lobbying against overprotective data protection measures that risk impeding research have been very strong messages because they come from the patients themselves.

The foundations are in place

The specific challenges of rare diseases have held back research and therapy development for decades. New technologies have introduced new challenges, in particular in terms of data analysis for next generation sequencing. Even so, we are now in a situation where all the ingredients that are needed to meet the bold IRDiRC aims of 200 new therapies and diagnostics for most rare diseases are coming into place. Research funders have recognised the issues and are committed to funding international collaboration. Technological advances have brought down costs, stimulated cutting-edge research and spawned new analysis tools. Large pharma have started to take an interest in rare diseases, and several companies such as Pfizer and GSK have opened rare disease units. Detailed legal and ethical work is addressing the challenges of data protection and moving towards risk-based models of consent where the perceived greater benefits of sharing results are set against the lesser risks of patient identification. The patient community is behind these new advances and strongly advocates sharing what is ultimately their own data. Achieving the data sharing goals will require a certain change in mindset on the part of the academic community, from the traditional approach of protecting results towards a culture of greater openness. But this seems to be the mood of the time, not just in the rare disease field: it has been tremendously encouraging to hear such strong support for these initiatives from leading labs globally and to see recognition of the fact that those who contribute and collaborate will themselves benefit later. The many different factors that are essential to progress in rare diseases are finally coming together – the foundations have been built and the rare disease landscape will certainly look quite different in 2020.

To find out how to get involved with these initiatives, please contact rachel.thompson@ncl.ac.uk

Links

www.irdirc.org – IRDiRC
www.rd-connect.eu - RD-Connect
www.rd-neuromics.eu – Neuromics
www.eurenomics.eu – EURenOmics
ec.europa.eu/research/horizon2020 – Horizon 2020

Translational genomics

Alain Li Wan Po, Lead Professional – Pharmacy and Pharmacogenomics, National Genetics Education and Development Centre.

On 15 January 2013, The National Genetics Education and Development Centre ran a meeting on Translational Genomics: the path from genomic insight to clinical applications, licensed drugs and treatment decisions through case-examples at the Royal College of Physicians.

The rationale for the meeting was that it's often perceived that genomic medicine is for the future. The Centre hoped to demonstrate that the future was already here by show-casing developments in use in the clinic as licensed medicines or interventions with demonstrated clinical efficacy.

In her blog posted after the event, Dr Kirsten Patrick, the Editorials Editor of the British Medical Journal articulated the need for everyone to have an understanding about genomic medicine by stating:

"Translational genomics, stratified medicine, personalised medicine…these are all concepts that I've had to try to get my head around since leaving medical school... Yesterday I had a crash course in translational genomics…We are ALL going to have to learn about genomic medicine, whether we're a clinician in a specialty where no gene-specific therapies seem to be on the horizon or at the forefront of delivering personalised medicine, and whether we're medically trained or lay. Personalised medicine is the future. Let's get our heads around it and help others to do the same"
(http://blogs.bmj.com/bmj/2013/01/17/kirsten-patrick-this-old-dog-learns-new-tricks-genomics/)

What is translational genomics?

Translational genomics refers to the exploitation of the information generated by research into the genetic make-up of the biological world for useful applications. In healthcare, this involves translating genetic insights for the development of new healthcare interventions, most notably, the development of:

- better drugs,
- improved disease prevention strategies
- better diagnostic methods.

The meeting brought together key-stakeholders in genomic medicine such as leading researchers making the discoveries to drug regulators; health technology assessors (NICE); health economists; practising clinicians; educators and patient representatives. This assembly recognises the fact that to maximise the potential gains of translational genomics, collaboration of all stake-holders is essential. Even at the industry level collaboration is necessary. Dr Mike Hardman, vice president of R&D Science Relations at AstraZeneca, commented, 'What's abundantly clear is that drug development in stratified medicine cannot be done entirely within one pharma house".

The meeting aimed to demonstrate that there was a continuum from gene to effector protein, and that therapeutic interventions could range from gene therapy (to replace or repair a defective gene) to improving the function of defective protein gene-products. This last point was illustrated by Dr Fredrick Van Goor's (Vertex, USA) talk on a novel cystic fibrosis drug (ivacaftor) that helps activate the cystic fibrosis transmembrane regulator (CFTR) in cystic fibrosis patients. Ivacaftor is now a licensed drug for patients having a specific CFTR mutation and a Phase II trial of a combination therapy with ivacaftor has just been completed with promising results for the more common mutation c.1521_1523delCTT/ (ØF508).

Pharmacogenetics at the patient interface

One area that holds particularly great promise is that of developing new drugs for prescribing according to the patient's genetic make-up, including somatic gene mutations. For example, in advanced countries, all women with breast cancer are now tested for specific tumour genetic abnormalities before being prescribed an intervention. Moreover, it is also possible to identify subjects who carry genes associated with greater risk of some cancers so that better targeted surveillance strategies can be developed for the individual patient and their close relatives.

Professor Munir Pirmohamed, NHS Chair of Pharmacogenetics, illustrated this aspect with an overview of the outcomes of research in this area, highlighting how:

- HLA-B*57:01 testing could identify most patients who should not be given the drug abacavir
- testing for variants of two genes (CYP2C9 and VKORC1) could potentially make warfarin-dosing safer
- testing for mutations in the gene BRAF, a gene encoding an intracellular signaling molecule, could identify likely responders to a new drug verumafenib that has transformed the management of metastatic melanoma.

Validating biomarkers

For every biomarker such as those that Munir Pirmohamed highlighted, there are a number that fail clinical validation tests. Even with CYP2C9 and VKORC1, the evidence is not robust enough for their testing to be required prior to prescribing warfarin. Dr Rose McCormack, of AstraZeneca described how biomarkers that seemed obvious at the start of a study may fail to be validated and that extensive work needed to

"The path from molecular discovery to a licensed drug therapy is a long expensive one"

be undertaken, ideally prospectively to ensure that a predictive biomarker be established. Such work eventually led to validation of epidermal growth factor receptor mutations as a response predictor for gefitinib, in a subgroup of patients with non-small-cell lung cancer.

Monoclonal antibodies

Monoclonal antibodies make up some of the most successful drugs on the market with a large number having annual sales of over $1 billion (blockbuster status). Professor Martin Glennie, Director of Cancer Sciences Division at Southampton University, illustrated how monoclonal antibodies can be harnessed to activate T cells to engulf cancer cells. Manipulation of T-cell co-receptors by monoclonal antibody targeting has already led to successful drugs such as ipilimumab for the treatment of advanced melanoma. Challenges remain on how to identify likely responders to such therapy. Although monoclonal antibodies were first introduced for therapeutic use many years ago, it is our view that the best is yet to come.

Big Pharma

In addition to Rose MacCormack and Mike Hardman from AstraZeneca, big pharma was also represented by Professor Lon Cardon, Senior Vice-President at GlaxoSmithKline. In his view, Pharma was "turning towards development of stratified medicine". He described the significant resources invested by GSK to develop such medicines for subgroups of patients; often so few in numbers that the drugs are referred to as orphan drugs.

Regulatory evaluation of genomic medicines

The path from molecular discovery to a licensed drug therapy is a long expensive one. Just how difficult the process is was illustrated by Dr Jörn Aldag of the small Dutch company UniQure, a company that grew out of a university spin-off through various transformations. He described the long arduous task of validating a gene therapy for lipoprotein lipase deficiency (the first to be licensed in the Western world), as regulators insisted on larger sample sizes even when the patients were just not there given the rarity of the condition. The expense led to the company going into liquidation before being rescued by venture capital. However, as Dr June Raine of the MHRA indicated, regulation is changing to take account of these difficulties to ensure that innovations can reach the market in a timely manner although clearly safety has to continue to be a prime concern.

Fair returns for innovators

It is estimated that taking a drug from scientific insight to the market costs well over £500m. Therefore, the prices charged by the innovators for their products are also high. A new drug targeting a specific cancer-cell abnormality (a targeted drug), typically costs over £10k per annum per patient. A prostate cancer vaccine can cost over £100k per course. Yet there is a need to ensure that the NHS gets value for money. Dr Elizabeth George, Associate Director of appraisals at NICE, described how NICE undertook a health technology assessment of a companion diagnostic that is required prior to use of a targeted drug. Such assessments are used to inform the NHS about the cost-effectiveness on genomic medicines. Professor Adrian Towse, Director of the Office of Health Economics, suggested that there may be a need to use different approaches for valuing genomic medicines that provided a lifetime cure (e.g a therapeutic cancer vaccine or gene therapy) to those that prolonged survival for a short time. Professor Bobby Gaspar from UCL's Institute of Child Health provided an example of a gene therapy, directed at severe combined immunodeficiency, that provided an apparent cure for some patients. He wondered whether industry would have an incentive to develop such therapies for such rare diseases (considerably rarely than the gene therapy for lipoprotein lipase deficiency that Jörn Aldag described).

Funding trials

The good use made of the generous donations of the public to advance drug research was illustrated by Professor Peter Johnson, Chief Clinician of Cancer Research UK, in his talk on the charity's coordination of major projects to validate biomarkers for stratified medicine, one of their areas of focus. In a major initiative that involves the UK government's technology strategy board, AstraZeneca and Pfizer, they hope to recruit 9000 patients with various solid cancers with a view to testing the feasibility of detailed gene sequencing in clinical practice to inform the management of a patient's personalised targeted treatment.

Future outlook

It is hoped that the meeting on 15 January 2013 showed that in many respects the future for genomic medicine is now. As Lon Cardon remarked in his talk, "personalised oncology medication isn't 'the future', it is happening today".The case-examples highlighted by the various speakers provided useful lessons on how we might become better at developing genomic medicines and rolling them out for the benefit of patients in as cost-effective a way as possible. Alastair Kent, a patient representative commented that optimising health gain from genomic medicines requires 'the creation of a framework where patients and families have a real role in establishing what matters about the condition and its impact on their lives'

For more information about this meeting, including videos of some of the presentations please visit www.geneticseducation.nhs.uk.

NIHR Collaborative Group for Genetics in Healthcare - update

James Brooks, Science Editor, BioNews on behalf of the NIHR Collaborative Group for Genetics in Healthcare

1. Two genes behind skull malformation condition identified

Scientists led by a team from Oxford University have identified mutations in two genes that lead to a serious skull condition.

People affected by the disorder, called craniosynostosis, are born with or develop abnormally shaped heads. This is caused by the plates of the skull joining together earlier than normal, which in turn can cause increased pressure in the skull and hearing, vision and breathing difficulties. Restricted brain growth and developmental problems are common.

Craniosynostosis affects around one in 2,200 children and in 21 percent of cases it is due to an identifiable genetic defect. But Andrew Wilkie, Professor of Pathology at Oxford University, the leader of the study, estimates that around a third of all cases are in fact caused by a genetic fault.

“I had the suspicion that there were other unidentified genes out there that were implicated and that still needed to be discovered”, he says, “and that's where this study has come in”.

The genes identified by the research have independent functions and this is reflected in the clinical picture. The non-bony tissues that join the skull plates are called sutures and only some of them will join too early in patients with craniosynostosis. “The two genes we identified affect the skull in very different ways and give distinctly different patterns of suture fusion from each other”, explains Professor Wilkie.

The research leading to one of the genes being identified began with DNA analysis of a family in which both children had craniosynostosis but its cause was unknown. The ERF gene was put forward as a potential candidate and this was confirmed when mutations in ERF were identified in an additional 11 samples from over 400 other patients, but not in analysis of healthy controls.

In most of these cases patients had been born with normally shaped skulls and the craniosynostosis only became apparent in early to middle years of childhood. On the other hand, patients with mutations in the other gene identified by the researchers, TCF12, usually required surgery within the first two years of life.

The researchers estimate that mutations in either ERF or TCF12 are responsible for up to three percent of all cases of craniosynostosis. In both cases knowledge of the genetic cause is helpful as families and care teams can better appreciate the characteristics and risks of the condition, including risks of inheritance.

But Professor Wilkie says that in the case of the ERF mutations, where the problem manifests later on, “knowledge of the mutation would be very valuable. It would alert a surgeon to the fact there was an underlying problem leading to the sutures not working properly. The surgeon would know to keep a very close eye on the child. They couldn't say that the child seemed fine and simply discharge them from follow-up”.

The research was partially supported by the National Institute for Health Research (NIHR). Professor Wilkie says that the NIHR's Comprehensive Clinical Research Network (CCRN) was essential to the success of the study which involved genetic information, resources and staff from four centres of excellence for craniosynostosis.

“Combined, those four centres represent a unique resource”, Professor Wilkie comments. “Before the NIHR-CCRN structure had been designed and put in place, it would have been impossible to have drawn on that resource as we did here”.

Both studies are published in Nature Genetics.
http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=7424

2. Bladder condition gene identified

A gene behind a rare bladder condition has been identified with potential implications for a far more common bladder problem affecting up to one percent of children.

The gene is the second to be linked to the rare and potentially fatal disease, called urofacial syndrome (UFS), and both genes were identified by scientists at the University of Manchester's Centre for Genetic Medicine.

“We estimate that around 80 percent of all cases of UFS are attributable to one of the two genes that we've now identified”, Dr Bill Newman, the leader of both studies, comments.

UFS is typified by two apparently incongruous characteristics. The first of these is a malfunctioning bladder which fails to fully expel urine, sending it back to the kidneys and damaging them. The second is a grimacing facial expression when smiling or laughing. UFS affects less than one in a million people worldwide.

In 2010, working with scientists in other international centres, Dr Newman's team pinpointed mutations in the HPSE2 gene as the cause of the syndrome in six families. In the current study, the researchers performed DNA analysis on a further three families - two Turkish and one Spanish - and identified mutations in the LRIG2 gene as being behind the condition in those cases.

The paper notes that there were 'no consistent clinical differences' between patients with changes in the LRIG2 or HPSE2 genes. Dr Newman says that future work will investigate the function of the LRIG2 gene. However, initial studies indicate that both

"Around one percent of prostate cancer patients will have the BRCA2 mutation"

genes are important in nerve development in the bladder.

With both genes involved in such an important biological pathway it seems likely they may be implicated in other conditions and Dr Newman's team are investigating this. Of particular interest are the estimated one percent of children who suffer from vesicoureteral reflux (VUR), when urine flows back toward the kidneys from the bladder.

"The appearance and behaviour of the bladder in VUR shows some similarities to what you see in UFS", says Dr Newman. "We have already shown that changes in LRIG2 are present in some cases of unexplained bladder and reflux dysfunction. So UFS might be one of these rare conditions that gives us insight into a much more common health problem".

Knowledge of the genes responsible in bladder dysfunction would in turn help with earlier diagnosis and could prevent kidney damage occurring. There may even be an impact on the kind of drug therapy used in those cases.

"Heparanase inhibitors are drugs that act in a similar way to the HSPE2 gene and have been studied in cancer treatment", Dr Newman explains. "If it turns out that HSPE2 is implicated in VUR then these drugs may be useful there. We're already looking at looking doing some studies to see if this could be the case".

The study is published in the American Journal of Human Genetics and is a National Institute for Health Research Clinical Research Network Portfolio study. http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=10796

3. Prostate cancer gene study should change treatment approach, say scientists

Prostate cancer patients who have inherited a well-known gene mutation are more likely to develop an aggressive form of the disease, a study shows.

It was already known that men carrying the BRCA2 mutation were at greater risk of prostate cancer. But research published in the Journal of Clinical Oncology shows that the cancers spread faster and are more often fatal in these patients.

As it can be difficult for doctors to determine whether newly diagnosed prostate cancer will be life-threatening, many patients are currently put under 'active surveillance' rather than put forward for immediate treatment.

But senior author Ros Eeles, Professor of Oncogenetics at the Institute of Cancer Research (ICR) says that NHS guidance should change to take into account the study's findings."It is clear from our study that prostate cancers linked to inheritance of the BRCA2 cancer gene are more deadly than other types", she said. "It must make sense to start offering affected men immediate surgery or radiotherapy, even for early-stage cases that would otherwise be classified as low-risk".

Around one percent of prostate cancer patients will have the BRCA2 mutation. Professor Eeles admits that without clinical trials it is impossible to be sure that this group of men would benefit from earlier treatment. All the same, she says, "the hope is that our study will ultimately save lives by directing treatment at those who most need it".

In the study researchers examined the medical records of 61 prostate cancer patients carrying the BRCA2 mutation as well as 18 patients with the related BRCA1 mutation and 1,940 non-carriers.

They found that when they received the diagnosis, men with either mutation were significantly more likely to have advanced stage cancer, or cancer that had already spread, than other patients. Crucially, patients with BRCA2 mutations were significantly less likely to survive the cancer, living an average of six and a half years after diagnosis compared with nearly 13 years for non-carriers. BRCA1 carriers also had reduced survival time, but this was not statistically significant.

Professor Alan Ashworth, chief executive of the ICR, said that the study illustrated how "knowledge of cancer genetics is now increasingly shaping the way we treat the disease, by allowing us to offer more intensive treatment, or even different drugs altogether, for people who have inherited cancer genes".

The study was a UK Clinical Research Network portfolio study (http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=4214), funded by the Ronald and Rita McAulay Foundation and Cancer Research UK.

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

If you think your research could benefit from the NIHR Genetics Specialty Group's services visit http://www.bsgm.org.uk/genetics-healthcare-research/ or email Dr Gill Borthwick, the Genetics National Research Coordinator, on Gillian.borthwick@ncl.ac.uk.

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

A new genetic model for cancer screening?

Philippa Brice, PHG Foundation

PHG Foundation and our partners in the COGS (Collaborative Oncological Gene-environment Study) Consortium have published a significant collection of papers in the March 2013 issue of Nature Genetics, which is a special edition focusing on the COGS Consortium's groundbreaking work advancing our understanding of the genetic epidemiology of cancer.

Many readers will be aware of the work of the PHG Foundation over the last few years as part of this major European Commission funded international collaboration. The COGS' research has been investigating genetic risk factors for common hormone-related cancers: breast, ovarian and prostate. It identified 41 new loci associated with breast cancer risk, 23 for prostate and three for ovarian cancer, as well as providing numerous clues to underlying disease mechanisms. As an organisation focused on the translation of genomic technologies into improved healthcare practice, our role in the project has been to lead work examining the implications of the research findings for health services.

In our commentary Public health implications from COGS and potential for risk stratification and screening, published as part of the collection in Nature Genetics, we set out how future cancer screening may be improved by the use of genetic information, but we also predict greater accuracy will come at the price of increased complexity.

Using modelling, the PHG Foundation-led team, which included colleagues from the Cambridge Institute of Public Health (CIPH) and University College London (UCL), found that adding genetic data could potentially enable greater discrimination between lower and higher risk groups, allowing stratification of screening so those genuinely at greatest risk are targeted.

On the flip side, delivery of such stratified screening would be more complicated than current age-based approaches, incorporating genetic testing and results into the risk assessment process and requiring differential care pathways for people according to different risk groups. Questions about the storage, access and privacy of the genetic data would also be likely to arise.

However, overall we conclude that the emerging results from genetic research can and indeed will be used to create new and improved stratified screening programmes, but they will require careful evaluation before widespread introduction, including consideration of the issues outlined here. Moreover, health professionals involved in all aspects of delivery of screening will need to understand the relevance and import of the genetic risk information and for this suitable education and expert support will be necessary.

PHG Foundation Director Dr Hilary Burton who led the work, commented: "For the last decade scientists have envisaged a future where Genome Wide Association Studies (GWAS) would lead to stratification of populations and improved prevention based on genetic susceptibility. This is the first time one of these major international studies has been associated with a parallel process using real results to investigate the potential impact on population health. Our conclusion is stratified prevention is possible and useful, but is complex. To achieve this vision of the future effective engagement between policy-makers, the public and the researchers is crucial".

Reference:

Public health implications from COGS and potential for risk stratification and screening.

Burton H et al. (2013) Nat Genet. 45(4):349-51.

The Indo-UK Genetic Education Forum Symposia- 2013

Shirley Hodgson, Professor of Cancer Genetic/Hon. Consultant Clinical Geneticist, St. George's Hospital Medical School, London

As a continuation of the previous three years Indo-UK Genetic Education Forum symposia, Dhavendra Kumar (University Hospital of Wales, Cardiff) led a group of us including myself; Gareth Evans (Manchester); Diana Eccles (Southampton); Eamon Maher (Birmingham); Meena Upadhyaya (Cardiff); Sian Ellard (Exeter) and Bert de Vries (Nijmegan) to the 2013 round of symposia across India (see table 1). Gareth, Eamon and Diana participated in the Mumbai and New Delhi meetings. In addition to the first two meetings, Dhavendra, myself and Meena also attended the third symposium in Lucknow. Sian Ellard and Bert de Vries joined us for the New Delhi and Lucknow meetings.

The conference in Mumbai (the Indian Cancer Genetics Conference) was the brainchild of Dhavendra and myself, as an educational three day event for geneticists, surgeons, gynaecologists and other health professionals in India, where Cancer Genetics is an emerging discipline. As we were developing the programme, there was increasing enthusiastic input from our local hosts at ACTREC (Advanced Centre for Treatment, Research and Education in Cancer), notably from the Director, Professor Rajiv Sarin, who included many local physicians and surgeons from many parts of India as speakers. We were privileged to meet Professor Shyam Agarwal from Lucknow, said to be the founder of Clinical Genetics in India, and many other local physicians and scientists. The programme thus became an inclusive one, allowing for exchange of ideas and an increasing understanding of the problems facing the discipline in different countries. From the perspective of the UK, we were impressed by how much the local geneticists and others involved in delivering the cancer genetics services had achieved in developing the discipline, and we gained some insight into the difficulties of offering the service to such an enormous population, and also what huge resources they had in terms of genetic isolates, different ethnic and socioeconomic groups. We were also able to see how far they had gone in developing biobanks and similar tissue/blood bank resources in the local campus, and to discuss genetic testing techniques and translational research.

Professor Sarin is developing an international cancer genome consortium (ICGC) which includes about 50 research projects in 24 different countries. They have completed the characterisation of 500 tumour samples and examined DNA and chromosomal changes in the tumours in relation to genomic DNA. Dr Kishore Amin has a large collection of tumour samples from oral cancers, predicated on the large number of such cases in certain regions of India due to the habit of chewing tobacco and betel nuts mixed with lime and calcium paste.

Although genetic counselling clinics are becoming established in India, training for genetic counsellors is not well established or recognised as a discipline there, so many professionals who wish to become accredited in genetic counselling go abroad for such training. It may be possible to develop a training curriculum which can be recognised at government level, by collaboration with UK cancer geneticists. Other areas where future collaboration between our countries may be profitable are collaborative research; help with developing management and counselling guidelines; ethical criteria and applications for ethical permission; genetic testing guidelines and consent forms; proformas for genetic test result reporting and other issues of common interest where debate may have been ongoing for some time in Europe. Methods of collaboration on the reporting and assessment of variants of unknown significance detected in India were discussed and could be facilitated by collaboration with UK molecular scientists.

Our hosts were very welcoming and hospitable, and we developed potentially long-lasting friendships which hopefully may lead to future collaborations. Our local hosts are initiating an Indian Society of Human Cancer Genetics, which aims to promote collaborative translational research; data sharing; service delivery; training; the development of guidelines and laboratory protocols; deliberations on ethical issues and consideration of the relevance to public health service delivery. We of course joined with enthusiasm!

The conference had organised some energetic evening entertainments, with wonderful food, where we had instruction on hand painting, watched bangles being made and witnessed the tireless energetic dancing of Professor Sarin (who said he did it to make his staff feel less scared of him!). We were very impressed by his stamina!

In New Delhi, the conference was entitled: The International conference on Next Revolution in Genetics and Genomics- Applications in health and disease, organised by Dr Ishwar Chander Verma, the Director of the Center of Medical Genetics. The remit of the conference was not confined to cancer genetics, which took up the first day of the programme; Next generation sequencing was the subject for day two, and prenatal and preimplantation genetic screening on the third day. The faculty comprised ourselves, and other international and national professionals. As in Mumbai, there was some opportunity for interaction and discussion, although sadly the programme was so full that there was no time for the

"...we developed potentially long-lasting friendships which hopefully may lead to future collaborations."

planned banquet, so more informal discussions were not possible! However, the sentiments of the group indicated a willingness to collaborate in the development of cancer genetics, with the same overall agenda as the Mumbai group.

The last conference of the Indo-UK genetic education collaboration was held in Lucknow, entitled Current trends in genetic and genomic medicine. This was directed by Professor M. C. Pant. This was short but well attended with lots of media interest and publicity that raised the profile of local academicians and health planners, eager to establish a leading genetics and genomics institute in Lucknow, the capital city of Uttar Pradesh, one of the large states of India. This is evident from the invitation extended by the Vice Chancellor of the King George's Medical University in Lucknow, one of the oldest medical and educational institutions of India.

The 2014 round of the Indo-UK Genetic Education Forum will commence from Lucknow followed by Bangalore, highlighting the best practices in clinical dysmorphology, ophthalmic genetics and genetic counselling. All those interested to join may contact Dhavendra in Cardiff (kumard1@cf.ac.uk).

Table 1: 2013 round of symposia across India

Indian Cancer Genetics Conference 23-25 January, 2013 Advanced Centre for Treatment Research & Education in Cancer, Tata Memorial Centre, Navi Mumbai.
Next Revolution in Genetics and Genomics- Applications in Medicine and Health 27-29 January, 2013 PGIMER Auditorium, Dr. RML Hospital, Baba Kharak Singh Marg, New Delhi.
Current trends in genetic and genomic medicine 31 January, 2013 Ram Manohar Lohia Institute of Medical Sciences, Lucknow, UP.

The UK Team with Professor Sarin, Director of the Tata Memorial Cancer Research Centre, at the Mumbai Indian Cancer Genetics Conference, 23-25 January 2013- from left Gareth Evans, Shirley Hodgson, Rajiv Sarin, Meena Upadhyaya, Anju Kumar, Dhavendra Kumar and Diana Eccles.

'Select incidental findings will be shared' – exome sequencing in the USA

Dr Anna Middleton, Wellcome Trust Sanger Institute, Cambridge

The UK Faculty in Lucknow, Current Trends in Genetic and Genomic Medicine, 31 January 2013: from left- Dhavendra Kumar, Sian Ellard, Shirley Hodgson, Bert de Vries and Meena Upadhyaya

Prof. Diana Eccles at the New Delhi symposium on Next Revolution of Genetics and Genomics, 27-29 January 2013.

The American College of Medical Genetics (ACMG) has recently published recommendations for reporting incidental findings (IFs) in clinical exome and genome sequencing. These advocate actively searching for a set of specific IFs unrelated to the condition under study. For example, a two year old child may have her exome sequenced to explore a diagnosis for intellectual disability and at the same time will be tested for BRCA mutations. The ACMG feel it is unethical not to look for a series of incidental conditions while the genome is being interrogated, conditions that the patient or their family may be able to take steps to prevent. This contradicts multiple international guidelines that advise against testing children for adult onset conditions. The ACMG justify this as "a fiduciary duty to prevent harm by warning patients and their families". They conclude that "this principle supersedes concerns about autonomy", i.e. the duty of the clinician to perform opportunistic screening outweighs the patients right not to know about other genetic conditions and their right to be able to make autonomous decisions about testing.

The ACMG acknowledge "there are insufficient data on clinical utility to fully support these recommendations… and… insufficient evidence about benefits, risks and costs of disclosing incidental findings to make evidence-based recommendations". Yet, they clearly felt the need to draw a line in the sand and create a starting point. This is a bold and fearless move. The result is that a set of conditions, genes and variants are listed, many of which will reveal uncertain pathogenicity in the absence of a family history.

The National Society of Genetic Counselors (US equivalent to our AGNC) has issued a Media Statement saying that the "NSGC applauds the efforts of ACMG providing guidance to laboratories and clinicians as we begin to integrate new genome sequencing technologies into clinical practice".

There is a serious lack of social sciences research that tells us what patients want from exome sequencing in the clinic never mind in a research setting. It will be interesting to see how the British clinical genetics community responds to the ACMG position. The topic has generated a number of online discussions, which can be accessed at

www.genomethicsblog.org

www.thednaexchange.com

www.genomesunzipped.org.

Update from NGRL Manchester

NGRL
National Genetics Reference Laboratory | Manchester

Andrew Devereau

NGRL Manchester provides four core services (DMuDB, SNPCheck, bioinformatic resource analysis and bioinformatic training), supported by related grant funding and consultancy. Project grant funding continues to be sought to support service provision beyond the next financial year.

In recent months NGRL Manchester has provided input into the development of the UK's 100,000 Genomes Project through the Chief Medical Officer's working groups and as part of the BSGM consultation. The team has also welcomed Nadeem Baig as Bio and Health Informatics Developer. Nadeem has a background in computer science, IT and bioinformatics and is currently focused on supporting and further developing SNPCheck.

DMuDB

DMuDB now has 56 subscribing laboratories from 22 different countries and significant amounts of data have been received from many of them. To keep up to date with new data, users can check the DMuDB home page for weekly reports, subscribe to DMuDB data alerts (email support@dmudb.net with 'subscribe DMuDB data alert' in subject line), and visit www.ngrl.org.uk/Manchester/page/dmudb-statistics to see a summary of data in DMuDB. UK laboratories continue to have free access to all data submitted by other UK laboratories; access to non-UK data requires a laboratory subscription. To find out more about subscription see the DMuDB login page https://secure.dmudb.net/ngrl-rep/Home.do or contact us at support@dmudb.net.

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

SNPCheck

SNPCheck continues to be widely used, with roughly 40,000 primer pairs being checked per month. Current development work is focussed on improving performance and adding minor features to improve the user experience.

To receive emailed news about SNPCheck as it is announced, users can sign up to the SNPCheck mailing list (www.ngrl.org.uk/Manchester/page/mailing-lists).

Bioinformatic tools

Reports and information on bioinformatic tools can be found on the NGRL website: www.ngrl.org.uk/Manchester/projects/informatics/bioinformatic-tools.

Training

NGRL and Nowgen are in the process of recruiting a new team member to lead the delivery of the popular bioinformatics training courses run for scientists and clinicians. The team has also been instrumental in the development of the curriculum for a clinical bioinformatics specialism in the Modernising Scientific Careers programme. This is scheduled for launch in September 2013.

Grant funded projects

GEN2PHEN – this project ends in June 2013. Work in the final stages has focused on two main themes –federation and sharing of variant data, and the collection of phenotype data.

EuroGentest – as part of this project NGRL delivered a workshop entitled The challenges of getting clinical data into databases. The workshop looked at the collection of clinical-quality data, including the need for phenotype data collection. Guidelines for data collections, system implementation, standardisation and quality control will be developed based on discussions and consensus reached during the workshop. Presentations from the workshop are available on the NGRL website: www.ngrl.org.uk/Manchester/page/eurogentest.

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

Familial hypercholesterolaemia (FH) paediatric register

Steve Humphries, University College London, London
Uma Ramaswami, The Willink Biochemical Genetics Unit, Manchester

FH is an autosomal dominant disorder, characterised by increased plasma levels of LDL-cholesterol (LDL-C) and premature Coronary heart disease (CHD). Heterozygous FH occurs in 1 in 500 of the population so ~120,000 people in the UK are thought to be affected of whom at least 75% are undiagnosed. Early identification of at-risk individuals allows effective statin treatment which significantly reduces CHD events and improves life expectancy.

In 2008 the National Institute of Clinical Health and Excellence (NICE) published a UK guideline for the identification and management of patients with FH (http://guidance.nice.org.uk/CG71). This guideline produced 109 detailed recommendations,1 several of which referred to DNA testing. All patients with a clinical diagnosis of FH were recommended to be offered a DNA test, firstly to confirm the diagnosis, and secondly so that this genetic information could be used in cascade testing. For children and young people with FH it was recommended that they should be seen by a specialist in an appropriate setting for this age group, and that children at risk of FH should be offered a DNA test by the age of 10 years if the family mutation is known, but otherwise diagnosis should be carried out by measurement of LDL-C. The use of a statin should be considered by the age of 10 years, although the age at which commencement of statins is recommended was open to clinical judgement.

While it is clear that statin treatment in adults has a good safety record, there are no long term studies of safety in children, with the longest studies usually not extending past two years, and restricted to following up lipid levels, growth rates, progression through puberty, and capturing information on any major side effects. Although the results of these short trials are reassuring, many clinicians are still reluctant to prescribe statins at an early age because of the lack of long-term data. It has been suggested that in some children with a modest elevation of LDL-C or where the age of onset of CHD in the family is later, it maybe clinically appropriate to withhold statin treatment until a child reaches adulthood, however data to address the long term CHD risk associated with this is lacking. Data on a surrogate measure of atherosclerosis development, namely the thickening of the carotid artery (determined by intima-medial thickness measurements) suggests that CHD is already developing at a young age. A Dutch study has demonstrated a significantly increased carotid artery thickening in FH children by the age of 10 compared to their non-FH brothers and sisters,2 that this thickening increases over time in FH children faster than in their non-FH siblings and that this increase can be significantly reduced (essentially to that in non-FH children) by treatment with Pravastatin.3

FH is known to be caused by mutations in three genes.4 In the UK ~93% of mutations are in the gene encoding the receptor for LDL-C removal (LDLR). About 5% of FH patients have a single mutation in APOB, which codes for apolipoprotein B the major apoprotein component of LDL-C that acts as a ligand for the LDL-C-receptor. A further 2% have a single mutation in PCSK9 which codes for proprotein convertase subtilisin/kexin type 9, a protein involved in the degradation of the LDL-receptor.5 Overall a mutation can be found in ~80% of patients with the strongest clinical suspicion of FH. Once identified, the mutation can be used for testing and identifying affected relatives. DNA-based cascade testing is a cost-effective method of finding additional FH patients,6 and has been used extensively in other countries in Europe (notably in Holland7) and, as shown in the 2010 UK audit (http://www.rcplondon.ac.uk/resources/audits/FH) in Scotland, Wales and Northern Ireland. In England, commissioning of DNA-testing and cascade testing has only been obtained by the South Central Cardiovascular Network, with blood samples being sent to Salisbury for genetic testing. Hopefully, with new commissioning groups being established, this will be the first of many.

This rise in children being identified provides the opportunity to establish an electronic register to monitor children with FH and to follow them into adult life. There are estimated to be at least 28,000 children and young people under the age of 18 with FH in the UK and the aim is to collect long term information on all of them. The register received Research Ethics Committee Approval on 30 January 2013 for a period of five years (REC reference 12/NE/0398). The database will comply with the Data Protection Act (1998), and all study data will be stored in a secure on-line database sited on a secure server at the Royal College of Physicians. Hospital clinicians will enter data on their own patients. No other database users, except members of the project team who have signed a confidentiality agreement, have access to these data. Clinicians who see children with FH in the UK are being asked to register their patients on a web-based database and update the information annually.

The work is being led by Steve Humphries (steve.humphries@ucl.ac.uk), Professor of Cardiovascular Genetics at University College London (UCL), and Uma Ramaswami (Uma.Ramaswami@cmft.nhs.uk), a Metabolic Paediatrician at the The Willink Biochemical Genetics Unit in Manchester. The Register is being hosted by the Royal College of Physicians, in collaboration with

"This rise in children being identified provides the opportunity to establish an electronic register to monitor children with FH and to follow them into adult life"

the Royal College of Paediatrics and Child Health, HEARTUK, the British Heart Foundation (BHF) and the British Inherited Metabolic Disease Group.

The aim of the Register is to:

- Monitor the effects of current and new treatments on growth, puberty, liver function and long term safety
- Provide comparative audit data
- Provide anonymised data for valid research in the field

A free mutation identification service by the BHF Cardiovascular Genetics Research Laboratory* at UCL, is being offered for any child registered on the database who has family mutation that has not been identified. The laboratory has a great deal of experience in screening for FH-causing mutations and interpreting the potential pathogenicity of novel mutations,8 and hosts the FH mutation database which lists more than 1200 different molecular causes of FH world-wide

The Register has a project manager, and an Executive and a Steering group which contains lipidologists, paediatricians, geneticists, epidemiologists, statisticians, staff in the clinical effectiveness unit as well as representatives of BHF and HEARTUK, the cholesterol charity. It also has advice and support from a patient representative Shrooti Thakerar, who comments "We are doing this so we can target which treatments are most effective for children and in so doing we hope to improve outcomes for continuing and future treatment.."

Members of the project team of the FH Register would be happy to visit centres where children with FH are being seen, to raise awareness of FH amongst paediatricians, and to provide guidance on clinical management of FH in children.

For more information go to (https://audit.rcplondon.ac.uk/PaedFH/Page.aspx?pc=homepage). If you see children with FH and would be willing to register your patients, subject to consent, click on the menu 'About the project' to download the enrolment form. Alternatively, contact the Project Manager at fh@rcplondon.ac.uk.

* CVG is a research laboratory, and therefore for use in future cascade testing we recommend that carriage of the identified mutation be confirmed in an accredited diagnostic laboratory.

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Fig 1. Screen shot of Data entry form

Royal College of Physicians — Setting higher medical standards
RCPCH Royal College of Paediatrics and Child Health
PAEDIATRIC FH REGISTER
HEART UK THE CHOLESTEROL CHARITY
Logged in user: admin

Familial Hypercholesterolaemia Proforma - Diagnosis

Instructions:

- Complete each section by clicking on the Section tabs at the top of the proforma.
- Once you feel each section is complete, it needs to be validated (click validate button), then you must save (click save button) the data before moving to the next section.
- The Section tab will become green indicating the section has been successfully completed.
- Remember to Save before you Exit.
- Not available - tick not available if the information is required is not known to you. That is, it is not recorded in the notes and is not available to you by other means.
- When all the tabs are green, the proforma is complete and valid, the data should be locked (ie can not be edited).
- There are help and comments icons to the right-hand side of each question. You can view any remarks you have made by clicking the 'View Comments' link

1. Diagnosis | 2. Assessment and treatment | 3. Lifestyle

1. DIAGNOSIS

1.1 What is the patient's diagnosis?
Definite Homozygous FH
Definite Heterozygous FH
Probable/Possible FH
Not available

1.2 Year of diagnosis? 2004 Not available

1.3 What were the lipid and lipoprotein measurements used to make the diagnosis?

Pre-treatment levels

Date	Fasting	Cholesterol (mmol/l)	HDL (mmol/l)	Trig (mmol/l)	LDL (mmol/l)	Lp(a) (mg/l)	Apo(B) (g/l)
09/10/2003	Yes / No	7.7	0.81	0.7	6.3		
Not available	Not available	Not available	Not available	Not available	Not available	Not available	Not available

1.4 At the first clinic appointment what was the patient's height and weight

Height (cm)? 79 Not available
Weight (kg)? 9.9 Not available
Birth weight (g) Not available
Gestational age (w)? Not available

1.5 Does the patient have a history of CHD? Yes / No / Not available

If yes this is substantiated by
a. Angiogram
b. Exercise ECG
c. Other (please specify)
Not available

1.6 Details of affected parent/relative (fill in only for **affected** relatives)

	Pre-treatment Cholesterol measurement mmol/l	Age onset CHD years	Tendon Xanthoma
a. Mother	Not available	Not available	Yes / No / Not available
b. Father	Not available	Not available	Yes / No / Not available
c. sister	25.35 Not available	Not available	Yes / No / Not available
d.	Not available	Not available	Yes / No / Not available
e.	Not available	Not available	Yes / No / Not available

1.7 Does the child have the clinical signs of:
a. corneal arcus? Yes / No / Not available
b. tendon xanthoma Yes / No / Not available

1.8 Has a family mutation been found? Yes / No / Not available

1.9 What is the family mutation, if known? (Please read help notes before completing this question) c.2054C>T p.(pro646Leu)

1.10 If the family mutation is known has the child been offered a DNA test? Yes / No / Not available

a. Month and Year when offered 17/03/2004 Not available

Clinical Bioinformatics Training

Angela Davies, Professional Training Manager - Nowgen

There are acute skills shortages in the workforce required to deliver the future benefits of genomic medicine1, particularly in light of the Government's recent announcements on the 100,000 Genomes Project. Because of the potential volume and complexity of data, the risk of mis-interpretation is high; therefore, appropriate bioinformatics training is required for current clinical scientists, clinicians routinely using genomic data and trainee clinical bioinformaticians to ensure patient safety and benefit is the highest priority. Training for the new profession of Clinical Bioinformatician is currently being addressed by the Department of Health (DH) through the development of the new Modernising Scientific Careers (MSC) Scientist Training Programme (STP) in Clinical Bioinformatics (Genomics specialism) due to commence in September 2013. Other specialisms are planned for roll out in 2014/15 including Physical Sciences and Biomedical Engineering and Health Informatics. Dr Angela Davies at Nowgen, with Professor Andy Brass from Computer Science at The University of Manchester and Andrew Devereau from the Manchester National Genetics Reference Laboratory (NGRL), are working with the DH to develop the curriculum for the new MSC programme in Clinical Bioinformatics. Recruitment to the Clinical Bioinformatics programme will be through the National School of Healthcare Sciences. Like the other STPs it will consist of a 3 year Masters course in Clinical Science, delivered through part-time blended learning at a University which will be integrated with work-based learning at the host genetic testing laboratory.

There is still a strong need for CPD training with a clear clinical focus to cover the use of bioinformatics tools, databases, Next Generation Sequencing pipelines and the infrastructure that is required to support such developments. Currently such training is typically delivered by academics with a strong interest/expertise in this area; however, there is now an urgent need to take a multidisciplinary approach in order to deliver a scalable training programme which is right for medical bioinformatics now and for the future. Nowgen, with the NGRL, have a long-established track record for the delivery of bioinformatics training in genetics and genomics to healthcare scientists and clinicians, most recently in a purpose-built bioinformatics training suite in The Nowgen Centre. Furthermore, Nowgen works closely with other partners, including The Centre for Genomic Research, University of Liverpool, The University of Manchester Core Bioinformatics Facility and also with industry, such as IDBS and Genomatix, to provide training in Next Generation Sequencing, with a particular focus on bioinformatics, for academics, clinical scientists and clinicians. Forthcoming courses can be found at: http://www.nowgen.org.uk/training/professional-training-events.php.

Reference

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Crisis Looming for Genetic Counsellors

The Genetic Counsellor Training Panel (GCTP)
Judy Tocher, Sheffield
Claire Dolling, Birmingham
Sue Kenwrick, Cambridge
Rhona Macleod, Manchester

Most of you will be aware of the tremendous success of the Genetic Counsellor Training Scheme1 which was established in response to the expansion of specialist genetic services proposed by the 2003 White Paper, Our Inheritance, Our Future2. In this paper, the Department of Health (DH) clearly acknowledged the need for appropriate skills and expertise within the NHS to support and take forward advances in genetic knowledge. The DH granted funds for expanding the training capacity for genetic counsellors and funding was obtained for up to 50 genetic counsellor training posts. The DH provided financial support for each trainee's salary, together with a generous educational allowance for the trainee and a stipend for the host department. On completion of the post, a trainee was expected to be ready to apply for registration with the Genetic Counsellor Registration Board (GCRB).

Over the first two phases of the scheme 43 trainees were appointed. Of these, 42 went on to work as genetic counsellors, of whom 38 have already gained professional registration with the GCRB. Of the nine trainees appointed in the third and final phase of the scheme, six have now completed their training and of these, five have secured employment as genetic counsellors. There are three trainees due to complete their training in 2013.

Feedback from trainees and hosting departments about the scheme has been overwhelmingly favourable, with trainees valuing the opportunity for professional development with structured training goals. Departments valued the monitoring role of the Genetic Counsellor Training Panel (GCTP) who reviewed the learning contracts drawn up by the trainee and their mentor, which formed the basis for the planned provision of training opportunities. The GCTP then monitored each centre to ensure that there were no obstacles to the trainee meeting their training obligations.

Traditionally genetic counsellors have been recruited from a diverse range of backgrounds. This has always been viewed as a strength of the profession and is something that the AGNC would like to see maintained. The main entrants into the profession either have a background in health or social services (the majority being nurses) or have completed an MSc in Genetic Counselling. Currently there are two accredited Masters degree courses in Cardiff and Manchester, producing around 15 graduates each year. It is of serious concern that future recruitment onto these courses may be inhibited without a clear pathway into the profession and in view of the recent significant increases in tuition costs.

The AGNC have worked hard to develop a clear career structure for genetic counsellors, which includes trainee genetic counsellors employed at Band 6. Centres advertising Band 7 posts have frequently found difficulty finding suitable experienced staff to appoint. Often, students graduating from the MSc programmes in Genetic Counselling do not have the required competencies to work without supervision. Applicants from a nursing background are, at appointment, lacking in the genetic skills and knowledge required for independent work without a period of training. This need will only increase as complex genetic information emerges from large scale genomic and exomic investigations. Hence there is a continued need for training posts and this position is fully supported by both the AGNC board and the GCRB.

The majority of genetic counsellors work in National Health Service (NHS) trusts with links to a regional genetic centre. Over the years, the day to day work responsibilities of genetic counsellors have evolved and genetic counsellors now have a great degree of professional and clinical autonomy. Although there are variations in working practice between regional genetic centres, most genetic counsellors now see patients and their families in their own clinics and have taken on some of the responsibilities previously undertaken by their medical colleagues. Genetic counsellors are also well placed to strengthen and further develop links with mainstream services and spread genetic knowledge. It is vitally important for clinical governance issues that only staff with the necessary skills and experience take on these responsibilities.

A recent workforce planning survey undertaken by the AGNC, including data from all the regional genetic centres, indicated that 29 genetic counsellors intend to retire in the next five years. With recent announcements of changes to pension arrangements and pensionable age, some genetic counsellors in post may, understandably, not yet have made their final decisions about when to retire. But the issue of filling these posts with suitably qualified staff remains.

The AGNC remain committed to genetic counsellor training but in the present economic climate it is extremely difficult for regional genetic centres, with decreasing budgets, to establish their own Band 6 training posts. Moreover fixed term posts become an easy target to meet service cost improvement goals. In a recent GCTP poll, concerns were expressed over the future funding of these posts and there was no certainty of continuation in future years.

Band 6 trainee posts are not only integral to succession planning within the

"Band 6 trainee posts are not only integral to succession planning within the profession but also bring tremendous benefits to individual host departments"

profession but also bring tremendous benefits to individual host departments. There are financially supported training schemes for the specialist registrars in clinical genetics and our colleagues in the laboratories receive funding through Modernising Scientific Careers. In order to have sufficient numbers of trained genetic counsellors with the skills and knowledge to deliver high quality genetic services in the future, we need to find a way to fund genetic counsellor training. We have a tried and tested system of Band 6 trainee posts with a proven record of success. We have a clear pathway to validate centres to ensure that they can provide suitable training opportunities and we have a willingness to continue to monitor training. What we lack is central funding to continue provision of training posts. The numbers required would be fairly small - an estimated 10 posts per year.

The risk of not embedding training posts in genetic counselling professional progression is that departments will have a deficit of sufficiently skilled staff and the quality of breadth of service we can provide will inevitably deteriorate. As genetic counsellors play such an important role in service delivery we must ensure they have the skills and competencies required. We therefore feel it is vital to both our profession and genetic services in the UK to find a way to fund trainee genetic counsellor posts in the future.

The Department of Health Training Panel is actively exploring ways to secure centralised funding. However, with current NHS cut backs and changes in the way genetic services are commissioned, the way forward remains unclear at present. We would welcome support from our medical colleagues in tackling this problem.

Comments and suggestions are welcomed: Please address correspondence to judy.tocher@sch.nhs.uk

References

1. Barnes C, Skirton H, Kerzin-Storrar L, Tocher J (2012) The Department of Health supported Genetic Counsellor Training Post Scheme in England: a unique initiative? J Community Genet 3:297-302

2. Department of Health (2003). Our inheritance, our future: realising the potential of genetics in the NHS. London, UK: Department of Health

An integrated genetics careers day delivered by the West Midlands Regional Genetics Laboratory

Georgina Hall, Clinical Scientist, WMRGL

On 15 February 2013 the West Midlands Regional Genetics Laboratory (WMRGL) hosted its third integrated genetics careers day. At the WMRGL we feel privileged to receive a vast number of requests for opportunities in genetics. Due to the high volume of such requests it was decided to host an annual careers day to give students an insight into the workings of a genetics laboratory and access to information on the different careers in genetics.

The morning session consisted of a series of talks detailing the work carried out by genetic scientists, technologists and counsellors along with a session based on careers in genetics. Students were given the opportunity to ask questions in an informal environment and to speak to a wide range of staff working in genetics.

In the afternoon a series of workstations gave students a taster of the work undertaken both at the laboratory and at the clinical genetics unit. The workstations covered both cytogenetic and molecular genetic aspects to reflect the integration of these two disciplines. Workstations included karyotyping and microarray analysis; principles of PCR and cystic fibrosis analysis; leukaemia genetics including diagnosis and monitoring and principles of genetic counselling.

The day ended with a tour of the laboratory, giving an insight into some of the techniques and machines in place as well as a snapshot of laboratory life. Factsheets were created and given to students which detailed important processes such as chromosome preparation. Attendance certificates were provided along with packs containing the WMRGL newsletter, pens and post-its.

Feedback from has been extremely positive with all students saying they would recommend the day. Many students commented that they didn't realise how many exciting careers where available involving genetics. All students were extremely grateful of being invited and were excited about being able to add this experience to their university applications. With the increasing demand for opportunities in genetics the WMRGL now aim to host these days biannually.

For further information please contact LabWorkExperience@bwhct.nhs.uk

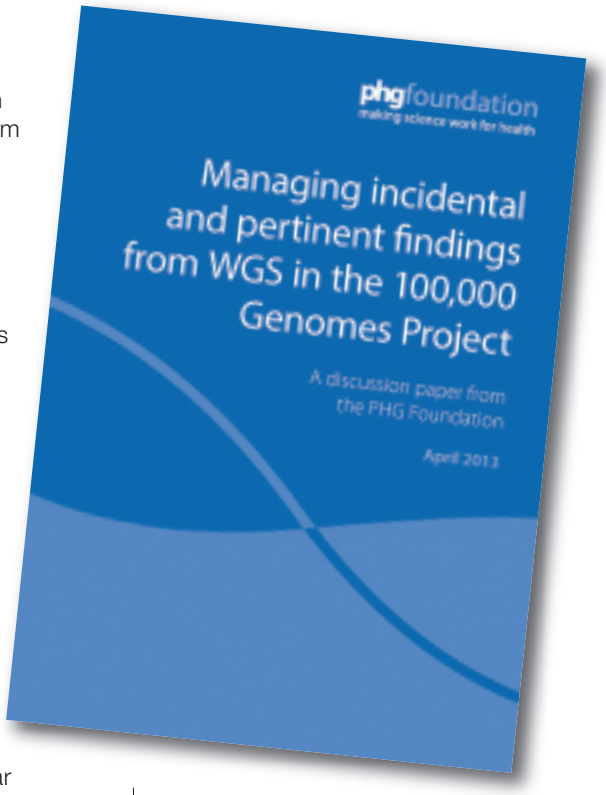
"A wonderful insight. Thank you for the experience"

"Thanks for a brilliant opportunity. A really well planned and organised day"

Handling incidental findings in the 100,000 Genomes Project

Alison Hall, PHG Foundation

The PHG Foundation has published recommendations on the management of findings from the Government initiative to sequence the genomes of 100,000 NHS patients. In Managing incidental and pertinent findings from WGS in the 100,000 Genome Project, The PHG Foundation advocates for a strong consent policy and restricting disclosure to only those results that are clinically actionable.



A framework for disclosure

The paper sets out an ethical framework for disclosing clinical and research findings to patients/research subjects. The starting point for the proposed framework is the need for clinicians and researchers to make a clear distinction between clinical and research elements of the project, as the ethical determinants of disclosure flow from this distinction. The proposed framework takes account of the extent to which findings (pertinent or incidental) emerging from clinical or research sequencing are reasonably likely to have a clinical impact on an individual's physical or psychological health.

Key recommendations include the need to seek consent for clinical and research elements of the 100,000 Genomes Project prior to taking samples for clinical use; and to contemplate only the disclosure of those findings that are scientifically and clinically significant, and which are serious enough to warrant further clinical intervention.

PHG recommends that the 100,000 Genomes Project participants be allowed to opt out of disclosure, although that option could be overruled in certain circumstances.

The paper can be downloaded at http://www.phgfoundation.org/news/13721/

Spotlight on the national lead genetic counsellors group

Janet Birch, Deputy Lead/Principal Genetic Counsellor, Cheshire & Merseyside Regional Genetics Service

The lead genetic counsellors group was the brainchild of Mandy Barry, Chair of the AGNC (2005-2007). Mandy recognised through her role as AGNC Chair and as Lead Genetic Counsellor (GC) for the Birmingham Service that there was no national forum for communication between the lead genetic counsellors of the regional clinical genetics services. The first meeting of the Lead GC Group was held in March 2007 and was funded by the AGNC Committee in order to address this gap and to allow opportunity for discussion of some of the many new challenges at the time. These included 18 week targets, workforce planning, GC recruitment & new employment legislation. The group has grown from strength to strength and is now completely independent from, but maintains close links with, the AGNC.

Lead GCs have a distinct role which includes professional leadership, management and recruitment in addition to operational responsibilities. This forum for sharing relevant information and experience has helped to promote national equity in both service delivery and in the GC profession/workforce and has become an invaluable arena for discussion and support for national lead GCs.

A key purpose of the group is to consider the demand and impact of changes in clinical practice, legislation and service delivery and to use their combined experience and 'real world' knowledge to respond, and to appropriately influence the national agenda and strategy. Lead GCs are in a unique position to oversee recruitment and ensure the maintenance of a competent, capable and appropriately qualified and registered GC workforce, to enable delivery of a safe, high quality genetic counselling service to patients in today's NHS. This is especially important as employers will be playing an increasingly significant role in this aspect of protecting the public owing to the introduction of new systems of regulation of health professionals by the current government.

Attendance at meetings is open to the lead GC for each regional clinical service/nominated deputy. The Chair's tenure is for three years. The group meets twice a year, in Spring at alternating locations across the UK and later in the year, by invitation at the AGNC Joint Meeting along with the GCRB and other current professional working parties. Issues arising during the year are also often addressed by group email discussion.

This year's Lead GC Group meeting in March was hosted by the Glasgow service. Agenda items included quality dashboards; the new Specialist Commissioning arrangements; designation of services; service specifications; national CQUINs (Commissioning for quality and innovation); The Francis Report and genetic counsellor regulation.

An email list for the group has been collated to include one nominated lead GC for each of the UK regional clinical genetics services. If you are the current lead genetic counsellor for your regional service and would like to join the email group or attend the meetings please contact the Chair of the Lead GC Group, Gail Mannion at gail.mannion@lwh.nhs.uk.

Service Developments

Cantú syndrome testing – a new service

Charlene Crosby, Clinical Scientist, Bristol Genetics Laboratory

A new diagnostic service for Cantú syndrome (OMIM #239850) is now available at the Bristol Genetics Laboratory (BGL). Cantú syndrome is a rare disorder characterised by congenital hypertrichosis, distinctive facial appearance, osteochondrodysplasia and cardiac features. To date 33 cases have been reported in the literature.

Cantú syndrome is an autosomal dominant/sporadic disorder with mutations in ABCC9 (OMIM *601439, also known as SUR2) identified in approximately 88% of patients with a clinical diagnosis. The ABCC9 protein is part of an ATP-sensitive potassium channel complex with mutations disturbing channel function.

The ABCC9 gene codes two transcripts: SUR2A (cardiac and skeletal muscle) and SUR2B (vascular smooth muscle and hair follicles). Both are encoded by 38 exons and the two transcripts differ only by the use of an alternative exon 38. Mutations in the exon 38* of SUR2A have been associated with dilated cardiomyopathy and atrial fibrillation.

70% of mutations identified in ABCC9 in patients with Cantú syndrome reside in exons 24-27 which encode the second transmembrane domain. As a first line test, sequencing of these four exons is now available at a cost of £215 within 40 days (urgent samples can be processed in 2 weeks). Full sequencing of the ABCC9 gene for patients where no mutation is detected in the first line test is currently under development and will be available later this year. Carrier testing and prenatal diagnosis is available for cases with a confirmed pathogenic mutation.

Referrals meeting UKGTN clinical testing criteria (congenital hypertrichosis and characteristic facial appearance) are accepted from clinical geneticists. Clinical advice is available from Dr Ingrid Scurr and Dr Sarah Smithson, Consultants in Clinical Genetics, at St Michael's Hospital, Bristol. A gene dossier has been submitted to UKGTN for review in the 2013/14 cycle.

For more information on this service, please use the contacts below.

References

Harakalova et al. 2012 Nature Genetics 44(7): 793-796.

Van Bon et al. 2012 The American Journal of Human Genetics 90: 1094 - 1101

Contacts

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Clinical Service
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Consultant Clinical Geneticists
St Michael's Hospital
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Bristol
BS2 8EG
Tel 0117 342 5653 / 0117 342 5316

Diagnostic whole exome and cancer gene panel sequencing in Leeds

David Cockburn, Leeds

Introduction

With the experience of over 3500 diagnostic next generation sequencing reports in the Leeds-based Yorkshire Regional Genetics Service, the centre now has validated and introduced its first services based on large gene panels and whole exome sequencing. The provision of whole exome sequencing within accredited NHS Regional Genetics Centres is in line with the BSGM's proposal to support the delivery of the 100,000 Genome Project in the NHS.

Cancer gene panel

For each patient, the clinician makes a selection from a menu of 18 cancer genes. The panel of genes is sequenced using Illumina sequencing technology and a bespoke Agilent SureSelect enrichment reagent. Results from the selected genes are interpreted and reported. This approach provides complete coverage for the defined genes (minimum sequencing depth 50x). Sanger sequencing is used to confirm pathogenic variants.

Validation was conducted testing 47 patients according to the above protocol (average seven genes per patient). Parallel testing was conducted for genes where diagnostic tests were already available in the Leeds laboratory using established technologies (in most cases by long-range PCR targeted NGS). Full concordance was observed for variants detected, indicating 95% confidence that the sensitivity is over 96% (excluding large rearrangements). Within the validation panel, pathogenic variants were found in 10/47 patients. These were within the genes: APC (1); BRCA1 (1); BRCA2 (4); MUTYH (1); SMAD4 (1); STK11 (1); and TP53 (1). Variants of uncertain pathogenicity were detected in only five patients.

To access testing, a request form including a gene menu is available. The initial service price is £860.

Whole exome sequencing

Diagnostic tests are being validated and introduced for four diagnostic referral categories:

- Primary ciliary dyskinesia (18 established loci with autosomal recessive inheritance)
- Meckel and Joubert syndromes (25 established loci with autosomal recessive or X-linked inheritance)
- Aortopathy gene panel (11 established loci with dominant inheritance, including major loci for Marfan and Loeys-Dietz syndromes)
- Cancer gene panel (extended panel of around 50 genes)

Full details for gene-sets investigated in each category are provided on request.

A diagnostic workflow has been established using the Agilent SureSelect All Exon kit. The strategy is to operate a universal workflow, which permits interpretation of large panels of genes where interpretation is feasible, and at a practical but clinically-helpful minimum depth of sequencing (around 90% coverage at 30x). Sanger sequencing is provided to confirm pathogenic variants. The data from whole exome sequencing data is retained, which will enable genes where phenotypic associations are identified at a later date to be interpreted at that time. A strategic advantage of whole exome sequencing is that once the universal workflows have been developed, it is relatively straightforward to adjust the gene-sets within services or introduce new services.

To validate diagnostic whole exome sequencing tests, samples are being tested from the four referral categories above with respect to quality criteria – in particular sequence quality and coverage for the relevant genes. Initial results for six primary ciliary dyskinesia patients were striking. Pathogenic mutations explaining the phenotypes were identified in four cases (each in a different gene).

Please enquire about availability of testing. The initial service price is £1250.

Research follow-up

Whole exome sequencing provides the possibility of sharing data not used for diagnostic tests with research groups. Where there is patient consent, and the referring clinician and a research group agree, data can be analysed for genes outside the scope of the diagnostic panel – e.g. for genes with indistinct genotype-phenotype correlations. This model is intended to be adopted for referrals for primary ciliary dyskinesia and Meckel syndrome, where research groups in Leeds have established links with the diagnostic lab.

Other next generation sequencing services in Leeds

The new services above are complementary to eleven established next generation sequencing diagnostic services at Leeds which are based on target enrichment by long-range PCR (outlined in BSHG newsletter Issue 46, pp44-47). By the end of March 2013, a total of 3551 diagnostic reports had been issued. A recent addition to this portfolio is a service for genes associated with cerebral malformations. Work is also well advanced at Leeds to introduce genome-wide copy number variation tests. A recent publication in Genomics is summarised elsewhere in this Newsletter.

Contact

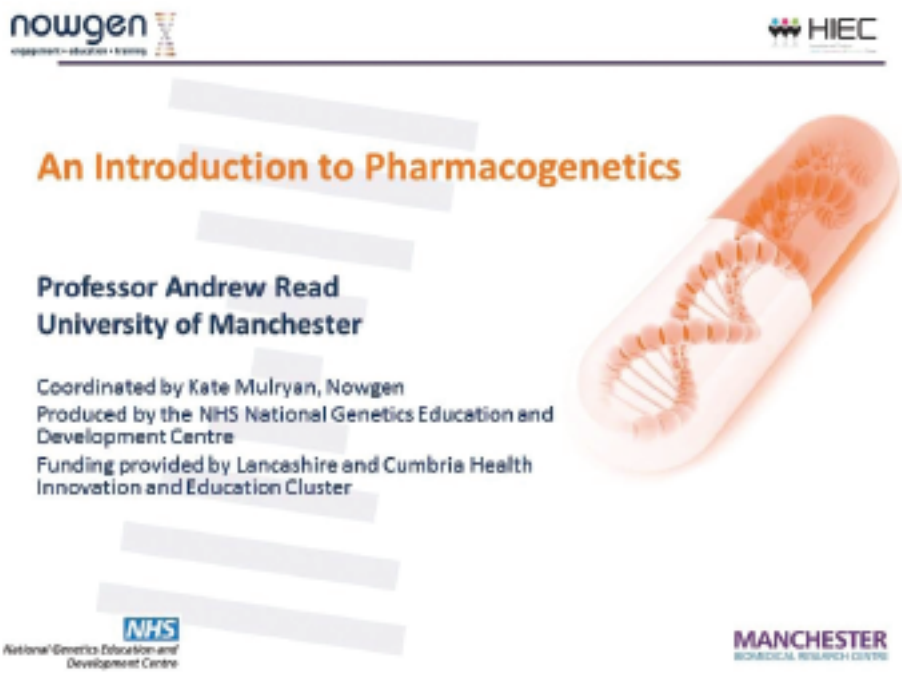
leedsdna@leedsth.nhs.uk
0113 206 5205

Noticeboard

E-learning in pharmacogenetics

Kate Mulryan, Nowgen, Manchester

Nowgen, in collaboration with the NHS Genetics Education and Development Centre (NGEDC), will launch a new e-learning course An introduction to pharmacogenetics in summer 2013. The course has been written by Andrew Read, Professor of Human Genetics at The University of Manchester, and gives a comprehensive introduction to pharmacogenetics, including a brief history, and several detailed case studies. The course will be freely accessible and will be available on the NGEDC website from July.



Me & my genes

Sue Malcolm, UCL

If you tell friends or family that you are a Geneticist, or even a Genetic 'Medicinist', you are likely to spark all sorts of questions. There is now a family friendly blog, Me & My Genes, from the Institute of Child Health at UCL which takes a light hearted view of how your genes rule your life.

To view the blog, visit:
blogs.ucl.ac.uk/clinical-molecular-genetics

If you would like to comment, suggest a topic, or write a guest blog, please contact Sue Malcolm at s.malcolm@ucl.ac.uk

BSGM
The British Society for Genetic Medicine

British Genetic Medicine Conference

16-18 September 2013
Arena and Convention Centre, Liverpool

Scientific Programme

BSGM Lecture: **"Genome Structural Variation, Disease and Evolution"** - *Professor Evan Eichler (Washington USA)*

Carter Lecture: **"Changing Lives: Stratified Medicine in Monogenic Diabetes"** - *Professor Andrew Hattersley (Exeter)*

Symposia:

Application of Genomic Technology for Improved Healthcare – *Professor Tim Hubbard (Cambridge), Professor Dr Peter Lichter (Germany), Dr Timothy Walker (Oxford), Professor Dennis Lo (Hong Kong)*

Clinical Bioinformatics - *Dr Christian Gillisen (Nijmegen), Dr Parthiban Vijayarangakannan (Cambridge), Professor Peter Robinson (Berlin)*

Current Trends in Inherited Cardiac Conditions - *Dr Clifford Garratt (Manchester), Professor Perry Elliott (Heart Hospital, UCL), Dr Arthur Wilde (Amsterdam)*

The Impact of Genomics on other Health Care Specialities - *Professor Nazneen Rahman (ICR, Sutton), Dr Elijah Behr (St. George's, London), Dr Hilary Burton (PHG Foundation, Cambridge)*

Next Generation Sequencing into the Clinic for Improved Cancer Diagnosis - Dr *Marco Gerlinger (London), TBC*

Developing Services in Genetic Counselling - *Dr Marion McAllister (Cardiff), Ms Melanie Watson (Southampton), Ms Georgina Hall (Manchester)*

Advances in Inborn Errors of Metabolism - *Professor Dr Ron Wevers (Nijmegen), Professor Dr Stefan Kölker (Heidelberg), Dr Paul Gissen (London)*

The reversibility of genetic disease - anabolic therapy to improve bone strength in Osteogenesis Imperfecta - *Dr Matthew Warman (Boston, USA)*

Association for Clinical Genetic Science Training - *Dr Chris Gibson (Birmingham), Dr Suzanne Chamberlain (Birmingham), Miss Laura Ions (Leeds), Dr Lowri Hughes (Birmingham), Mr Nicholas Hickson (Manchester)*

Practical Research in Genetic Healthcare - *Professor Sir John Burn (Newcastle), Professor Julian Sampson (Cardiff), Professor Andrew Wilkie (Oxford), TBC*

Understanding the Processes Driving Mutation in the Human Genome - *Dr Celia May (Leicester), Professor Adam Eyre-Walker (Sussex), Dr Anne Goriely (Oxford)*

Workshops:

Quality Issues for Diagnostic Laboratories - *Dr Sandi Deans (UK NEQAS) / Dr Simon Patton (Manchester), Dr Ros Hastings (Oxford), Mr Chris Mattocks (Wessex), Mr Eddy Maher (Edinburgh), Dr Fiona Macdonald (Birmingham)*

Genotyping in Cancer - Insights into Aetiology, Function and Clinical Applications - *Professor Alvaro N Monteiro (Florida, USA), Dr Antonis Antoniou (Cambridge), Dr Clare Turnbull (ICR, Sutton), Professor Ros Eeles (ICR, Sutton)*

Treatment of Genetic Disorders - *Dr Laurence Legeai-Mallet (France), Dr Annemieke Aartsma-Rus (the Netherlands), Mr Dominic McMullan (Birmingham)*

Education:

NGS: A Journey through the Bioinformatics Pipeline - *National Genetics Reference Laboratories*

Communicating Genetics - *National Genetics Education and Development Centre*

Debate:

"This house believes incidental findings should never be fed back to patients following Exome Sequencing"
Professor Martin Bobrow (Cambridge), Professor Mike Parker (Oxford), Professor Art L Beaudet (Houston, USA)

Plenary and concurrent sessions from submitted papers

BSGM, Clinical Genetics Unit, Birmingham Women's Hospital, Edgbaston, Birmingham B15 2TG
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Registered Charity No. 1058821

British Society for Genetic Medicine/ British Society for Human Genetics Annual General Meeting

Monday 16 September 2013 at 17:30 at the British Genetic Medicine Conference to be held at the Arena & Convention Centre, Liverpool

Agenda

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 5 August 2013 email: adam.shaw@gstt.nhs.uk

Welcome to New Members

15 new members were elected to the British Society for Genetic Medicine in January 2013

Dr Stuart Gillies	ACGS
Mrs Sharon Jenkins	AGNC
Dr Helen Alabede	BSGM
Dr Aseel Al-ansari	BSGM
Dr Musallam Said Al-Araimi	BSGM
Miss Joanne Davies	BSGM
Miss Jennie Sara Dring	BSGM
Mr Jamie Ellingford	BSGM
Mrs Tania Senior-Mckenzie	BSGM
Dr Emma Killick	CGG
Dr Catherine Dennis	CGS
Dr Muriel Holder	CGS
Dr Jane Emily Hooper	CGS
Dr Arveen Kamath	CGS
Dr Winnie Peitee Ong	CGS

Travel awards

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

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

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

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

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

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

Conference Reports

The deadlines for applications are:

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

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

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

An application will generally require:

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

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

Keystone Symposia Conference- Non-coding RNAs in development and cancer. 20th-25th January 2013.

Josie Hayes. Translational Neuro-oncology Research group, Leeds Institute of Molecular Medicine, St James's University Hospital, Leeds, LS9 7JT

I am very grateful to the BSHG for part funding my trip to Vancouver, Canada to present my work as a poster presentation at the Keystone Symposia Conference on Non-coding RNAs in Development and Cancer in January 2013.

The meeting was well worth the visit, and I forged invaluable contacts during my stay, as well as learning important aspects on non-coding RNA, which will be of benefit to my PhD.

The conference focused on current studies to discover non-coding RNAs and elucidation of their interactions. There were also a number of presentations on regulation, biogenesis and function of both long and short non-coding RNAs delivered by key leaders in the field.

A number of industrial presenters announced how far we are with microRNA therapeutics, with the possibility, all being well, of a microRNA therapeutic available for treatment in March next year. Other companies are also well ahead with the identification of serum and CSF microRNA markers for patient stratification in this age of personalised medicine.

The conference had a very positive vibe, with numerous collaborative opportunities made between all levels of academic scientists, industrial scientists and clinicians from the world over. The meeting provided me with some ideas for the work I was presenting; microRNAs associated with survival in Glioblastoma, and also stirred up some ideas for other researchers in the field.

During my time in Vancouver I took the opportunity to visit Professor Marco Marra, the Director of the British Columbia Cancer Agency Genome Science Centre. This laboratory provides some of the data for The Cancer Genome Atlas; a data portal which my PhD work up to now has been based on. During my visit they provided me with invaluable information and tips for the microRNA sequencing I'm embarking on.

In summary, this trip was highly inspirational in the first year of my PhD and I am extremely grateful to the BSHG, Marie Curie and Keystone Symposia for the opportunity to attend, and present at this meeting.

Forthcoming conferences

Integrating Cancer Genetics into Routine Clinical Practice: 06 June 2013
Venue: The Education and Conference Centre, The Royal Marsden Hospital Stewart's Grove London
Organiser: Institute of Cancer Research and The Royal Marsden NHS Foundation Trust (conferencecentre@rmh.nhs.uk)
Website: www.royalmarsden.nhs.uk/genetics

(ESHG) European Human Genetics Conference: 08-11 June 2013
Venue: Palais des Congrès, 2 Place de la Porte Maillot, 75017 Paris, France
Contact: conference@eshg.org
Website: www.eshg.org/eshg2013.0.html

Fundamentals of Next Generation Sequencing: 18 June 2013
Venue: The Nowgen Centre, Manchester
Organiser: Kate Mulryan (training@nowgen.org.uk)
Website: http://www.nowgen.org.uk/facilities/events/event.php?id=51

Immunity to infection and immunodeficiency: fundamental and clinical aspects explored: 19 June 2013
Venue: The Royal College of Pathologists, 2 Carlton House Terrace, London SW1Y 5AF United Kingdom
Organiser: Leon Pein (leon.pein@euroscicon.com)
Website: http://www.regonline.co.uk/infection2013

Functional Genomics and Systems Biology: 19-28 June 2013
Venue: Wellcome Trust Genome Campus, Hinxton, Cambridge, UK
Organiser: Wellcome Trust Advanced Courses (advancedcourses@hinxton.wellcome.ac.uk)
Website: www.wellcome.ac.uk/Education-resources/Courses-and-conferences/Advanced-Courses-and-Scientific-Conferences/Advanced-Courses/WTX026850.htm

Introduction to NGS bioinformatics: 19 June 2013
Venue: The Nowgen Centre, Manchester
Organiser: Kate Mulryan (training@nowgen.org.uk)
Website: http://www.nowgen.org.uk/facilities/events/event.php?id=63

(ISABS) 8th ISABS Conference on Forensic, Anthropologic and Medical Genetics: 24-28 June 2013
Venue: Split, Croatia
Organiser: International Society for Applied Biological Sciences (ISABS) (info@isabs.hr)
Website: http://www.isabs.hr/

5th International Congress of Molecular Medicine: 27-30 June 2013
Venue: Firat Universty, Elazig city, Turkey
Organiser: Turkish Society of Molecular Medicine (molecular2013@conplus.org)
Website: http://www.molecular2013.org

The Leena Peltonen School of Human Genomics: 18-22 August 2013
Venue: Wellcome Trust Conference Centre, Wellcome Trust Genome Campus, Hinxton, Cambridge
Organiser: Manolis Dermitzakis University of Geneva, Switzerland Jeffrey Barrett Wellcome Trust Sanger Institute, UK Mark McCarthy Oxford University, UK (laura.hubbard@wtgc.org)
Website: https://registration.hinxton.wellcome.ac.uk/display_info.asp?id=345

The Genomics of Common Diseases 2013: 7-10 September 2013
Venue: Keble College, Oxford, UK
Organiser: l.hubbard@hinxton.wellcome.ac.uk
Website: https://registration.hinxton.wellcome.ac.uk/display_info.asp?id=347

(BSGM) British Genetic Medicine Conference: 16-18 September 2013
Venue: Arena and Convention Centre, Liverpool
Contact: Dina Kotecha (bshg@bshg.org.uk)
Website: www.bsgm.org.uk / http://bgmc2013.bshgconferences.org.uk/

(HGV2013) 14th International Meeting on Human Genome Variation and Complex Genome Analysis: 30 September-02 October 2013
Venue: JW Marriott Hotel, 19-3 Banpo-dong, Seocho-gu, Seoul, South Korea
Website: http://www.hgv2013.org/home/

Mitochondrial Disease: translating biology into new treatments: 2-4 October 2013
Venue: Wellcome Trust Conference Centre, Hinxton, Cambridge, UK
Organiser: L.criddle@hinxton.wellcome.ac.uk
Website: https://registration.hinxton.wellcome.ac.uk/display_info.asp?id=349

(ASHG) American Society for Human Genetics Annual Meeting: 22-26 October 2013
Venue: Boston Convention & Exhibition Centre, Boston, MA, USA
Contact: ashgmeetings@ashg.org
Website: http://www.ashg.org/2013meeting/

Epigenomics of Common Diseases: 7-10 November 2013

Venue: Wellcome Trust Conference Centre, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK
Organiser: l.hubbard@hinxton.wellcome.ac.uk
Website: https://registration.hinxton.wellcome.ac.uk/display_info.asp?id=356

The Fourth Cardiff Symposium on Clinical Cardiovascular Genetics: 21-22 November 2013

Venue: Cardiff, South Wales. UK
Organiser: The Wales Gene Park, Cardiff University, Angela Burgess Education & Project Manager (burgessam@cf.ac.uk)
Website: http://www.wgp.cf.ac.uk/ProfessionalEducationEvents.htm

BSHG News Editor

Deadline for contributions for next issue is 30 November 2013

BSHG Editor: Michelle Bishop PhD

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Editorial

As we go to press, it seems that Spring has finally Sprung (or is at least on the run-up to the vaulting horse) and we can say goodbye to winter. Goodbye too, to The Probe; and hello 'ACGS Section of the BSGM Newsletter'! Well, snappy it ain't, but quality, it is! Thanks to all the contributors to this edition: a wide range of topics are presented, coming from the former disciplines of cytogenetics and molecular genetics. First up is the study by Josie Hayes and colleagues on the use of Next Generation Sequencing and array CGH in the detection of Copy Number Variants. They conclude that NGS is the way forward but their thinly veiled advert suggests that prices start from £250. Speaking of adverts, this issue contains important announcements concerning new service developments in Joubert syndrome and inherited ataxias (by NGS). In addition, there are calls for new NEQAS assessors, as well as for candidates and facilitators for the FRCPath study groups. Yes, your association needs you!

We have two reports from conferences attended by fortunate recipients of ACC travel grants, in the fields of cancer genetics and cytogenetics (Sophie Laird), and CNS malignancies (Josie Hayes). And finally, but by no means least, Martina Owens and Sian Ellard report on the last ever CMGS Scientific Sub-Committee Study, in the area of EFGR testing. Enjoy this issue and keep the articles coming!

Martin Schwarz

Diagnosis of Copy Number Variation by Illumina Next Generation Sequencing is comparable in performance to Oligonucleotide Array Comparative Genomic Hybridisation

Diagnosis of Copy Number Variation by Illumina Next Generation Sequencing is comparable in performance to Oligonucleotide Array Comparative Genomic Hybridisation

The aim of this project was to determine whether Next Generation Sequencing (NGS) would be an appropriate test to be used in the diagnosis of developmental delay and learning difficulties in children.

Detection of copy number using the BlueGnome 8x60K oligonucleotide array comparative genomic hybridisation (aCGH) platform was compared with low resolution NGS using the Illumina GAIIx on 39 patients referred to the Leeds Clinical Cytogenetics Laboratory with developmental delay and/or learning difficulties.

NGS analysis was performed by comparing the number of sequence reads in non-overlapping windows between patient and control samples using custom built software. This software is available as supplementary material to the publication.

All eleven clinically significant imbalances detected by aCGH and confirmed by FISH or Quantitative PCR (q-PCR) were also detected by NGS. In addition, the NGS technique called one purported pathogenic copy number variant (CNV) that was not detected by aCGH and was confirmed using q-PCR. This was a 49Kb deletion outside of the targeted areas of the array (2q23).

Non-pathogenic, unconfirmed copy number calls were detected by both platforms; however few were concordant between the two. This is likely due to the different controls used on the two platforms.

The workflow of the NGS is currently more laborious than that for aCGH, but could be automated and would integrate well with proposed future testing by NGS in our diagnostic laboratories. Lower quality and quantity DNA could be tolerated in the NGS pipeline and more uniform coverage of the genome is obtained. The test can also be tailored to the appropriate requirements for the sample if necessary. We conclude that NGS would be a suitable test for detection of CNVs in the appropriate setting.

The Leeds Cytogenetics Laboratory is currently costing this method (with prices from £250 per sample) and welcome any interest in this service for cases where standard aCGH has failed. Please contact Sarah Hewitt (sarah.hewitt@leedsth.nhs.uk) if you wish to express interest.

Reference

Hayes JL, Tzika A, Thygesen H, Berri S, Wood HM, Hewitt S, Pendlebury M, Coates A, Willoughby L, Watson CM, Rabbitts P, Roberts P, Taylor GR. Genomics. 2013 Apr 15; S0888-7543(13)00069-4.

Comparing methods for EGFR mutation testing in non-small cell lung cancer: the last CMGS Scientific Sub-Committee study!

Martina Owens and Sian Ellard, Exeter

EGFR mutation testing of tumour samples is available in more than 20 UK laboratories for predicting sensitivity to treatment with tyrosine kinase inhibitors (e.g. erlotinib and gefitinib) for patients with non-small cell lung cancer. Multiple different techniques are routinely used, which can be broadly divided into two sub-groups; screening (e.g. Sanger sequencing and pyrosequencing) or targeted (e.g. real-time PCR assays, ARMS). The aim of the study was to compare the sensitivity of these methods for the detection of two EGFR mutations, p.Leu858Arg (p.L858R) and an exon 19 deletion, c.2235_2249del. The p.L858R mutation and deletions within exon 19 of the EGFR gene account for ~90% of mutation positive cases.

An invitation to participate in the study was sent via the CMGS Heads of Labs and 14 laboratories requested samples for testing. Each lab was sent coded samples with varying mutation loads (from 0-15%) to be tested for the two mutations. Eleven laboratories used their standard testing method(s) and returned 15 sets of results for the p.L858R samples and 10 for the exon 19 deletion. The p.Leu858Arg (p.L858R) mutation was detected at levels between 1 and 7.5% by Sanger sequencing, pyrosequencing, real-time PCR, ARMS and CE-SSCA. The c.2235_2249del mutation was detected at 1-5% by fragment size analysis, Sanger sequencing or real-time PCR. A mutation was detected in 24/25 (96%) of the samples tested which contained 5% mutated DNA. The 1% sensitivity claimed for commercial real-time PCR targeted EGFR tests was achieved and our results show greater sensitivity for the Sanger sequencing and pyrosequencing screening methods compared to the 10-20% detection levels cited on clinical diagnostic reports. We concluded that multiple methodologies are suitable for the detection of acquired EGFR mutations.

This work will soon be published in Diagnostic Molecular Pathology. We would like to thank all the laboratories who participated in this study.

Conference Reports

1st International Workshop on Cancer Genetic & Cytogenetic Diagnostics 20-22 March 2013, The Netherlands

Sophie Laird, Pre-Registration Clinical Scientist, Wessex Regional Genetics Laboratory

Nijmegen, the oldest city in The Netherlands, was the location for the (long awaited) 1st International Workshop on Cancer Genetic and Cytogenetic Diagnostics. This three day workshop brought an international group of diagnostic geneticists, clinical healthcare professionals and researchers together for an informative and interactive overview of many aspects of cancer genetics.

The presentations selected gave delegates a whistle stop tour of 30 years of cancer cytogenetics of malignancies including karyotyping, fluorescence in situ hybridisation (FISH) and cytogenetic nomenclature. Reflecting the technical advances of genetic diagnostics, presentations delivered discussed microarray based genomic profiling and the use of new technologies to sequence single genes, panels of genes or whole exons. Particularly useful were Jacqueline Schouman's (Lausanne University Hospital, Switzerland) talk on array profiling in oncology at a time when professional guidelines for this technique have not yet been established and Torsten Haferlach's (Munich Leuakemia Laboratory, Munich) talk on his experience of automation and practical applications of next generation sequencing. Bauke Ylstra (VU University Medical Centre [VUmc], Amsterdam) also provided an interesting account of shallow, whole genome sequencing of DNA from formalin fixed paraffin embedded (FFPE) solid malignancies in order to detect the clonality of multiple tumours from a single patient. Disease-specific talks were also presented that outlined established cytogenetic subgroups within different malignancies and discussed the use of MLPA, high-resolution SNP array analysis and next generation sequencing within a number of diseases and how these techniques have allowed the identification of a number of additional genetic aberrations. The spoken presentations were opened and closed by Ros Hastings (United Kingdom Cytogenetic European Quality Assessment for Clinical Cytogenetics, Oxford University Hospitals NHS Trust) who gave thought provoking talks enforcing the importance of validation of new techniques and continuing quality assurance to ensure correct patient management.

Photograph of organisers, speakers and delegates.

The tone of the entire workshop was relaxed and attendees were free to ask questions and interact with the speakers- often leading to discussions comparing working practices. Practical workshops provided a platform to work through a selection of case scenarios and there were also concurrent sessions on data analysis provided by analysis software vendors.

Whilst this workshop is still in its infancy, the organisers Marian Stevens-Kroef, Eva van den Berg and Berna Beverloo successfully provided a well thought out programme and I would recommend this workshop to other trainees and those wishing to develop laboratory contacts and/or consolidate their knowledge in Cancer Genetics. I must sincerely thank the ACC for part funding my attendance through the ACC travel fund.

EORTC-EANO-ESMO 2013 conference: Trends in central nervous system malignancies. 22-23 March 2013, Prague

Josie Hayes, Translational Neuro-Oncology Research group, Leeds Institute of Molecular Medicine

I had great pleasure in attending the EORTC-EANO-ESMO 2013 conference in Prague in March 2013 and I'm very grateful to the ACC for part funding my trip. I presented the results of my study in poster form which used microRNA and gene expression datasets from The Cancer Genome Atlas to identify pathways involved in patient prognosis.

The meeting was a great success and provided me with valuable information on the current trials in the field and different European practices for diagnosis and treatment. There were basic development presentations on 1p19q testing and what genes could be behind the prognostic effect of this combined loss. IDH mutation status was a prominent topic and the possibility of using it as a therapeutic target was discussed.

A session was designated for diagnosis and prognosis with speakers focusing on when to test for BRAF fusions and mutations and how to follow up glioma patients with MR imaging. Professor Monika Hegi (Switzerland) also presented on the importance of the distinct epigenetic context created by IDH1 mutations (CIMP), and how the association of this with MGMT methylation will provide a better understanding of different treatment response patterns.

There were sessions dedicated to the management of all grades of glioma, metastatic brain cancer and rare tumours. Current clinical trials were covered as well as debates on controversies in the area.

In summary this conference was highly educational and opened discussions of my work with people of many different disciplines in neuro-oncology. I'd like to thank the ACC for providing me with the opportunity to present at this meeting.

FRCPath Part 1 and Part 2 Study Groups

Richard Barber

For the last two years a team from the West Midlands Regional Genetics Laboratory has successfully organised the FRCPath Part 1 and Part 2 self-help revision courses for both Cytogenetics and Molecular Genetics candidates.

We are now asking for expressions of interest from candidates wishing to attend the courses and facilitators to help review Part 1 candidates' notes.

Part 1 - Candidates

An initial meeting to be held in June 2013 (date to be confirmed) in Birmingham will provide an introduction to the course, the exam and an opportunity to review the content of the course to ensure recent developments have been included. Previously successful candidates will be available to give their experience of revision and the exam.

For those candidates who wish to take part in the course after the initial meeting, timetables for the Cytogenetics and Molecular Genetics courses will be distributed. The courses are divided into seven sessions and run on a monthly basis starting in July 2013 and ending in January 2014. The participants are required to either review notes from the previous year or write a new 2-4 page set of notes for one topic in each session and submit them by the timetabled deadline. All notes are uploaded onto a password protected dedicated website using a personal login. The website also provides a discussion forum for participants and facilitators to communicate.

Essay titles are also set by the facilitators and candidates produce essay plans (one page of bullet points) for each session.

If you are interested, please contact bhamrgltraining@bwhct.nhs.uk specifying which course, molecular or cytogenetics, you are interested in.

Part 1 - Facilitators

If you have been successful in passing the FRCPath Part 1 exam and would like to help others achieve this then please consider volunteering to become a facilitator. The role requires you to review notes and essay plans and provide short feedback on their content. There is no travel necessary and the role should not take more than a few hours of your time.

If you are interested, please contact bhamrgltraining@bwhct.nhs.uk specifying which course, molecular or cytogenetics, you would be able to help with

Part 2 - Candidates

As well as supporting the Part 1 self help course we are willing to support some Part 2 preparation sessions. These will bring candidates from both cytogenetics and molecular genetics together in an informal environment to share knowledge in the main areas of our laboratory service, focussing on the science, the application of the science, and management. An examiner will also be there to guide participants through discussions. The sessions would promote and encourage open discussion rather than formal presentations.

If you would like a self help course to be arranged for Part 2 preparation to run during Jan/Feb/March 2014 please contact Jennie Bell via our training email

UK NEQAS for Molecular Genetics

Sandi Deans

The UK NEQAS for Molecular Genetics Scheme would like to invite you to act as an EQA assessor for the annual assessment of the molecular core diseases. We aim to include representatives from a range of laboratories in order to include the views of as many participants as possible. The EQA marking process takes place throughout September and October and the role of assessor is open to all who routinely authorise molecular genetic reports. If you are interested in acting as an EQA assessor or would like further information then please contact the Scheme Director, Dr Sandi Deans on Sandi.Deans@ed.ac.uk.

Next Generation Sequencing Services

Penny Clouston, Oxford

The Oxford Regional Genetics Laboratory is launching two next generation sequencing services for 1) Joubert syndrome and 2) Inherited Ataxias.

Both panels use Agilent's Haloplex Targeted Enrichment system to capture regions of interest (ROI) and Illumina's MiSeq platform to perform the next generation sequencing. Complete bioinformatic analysis is undertaken to identify pathogenic variants which are confirmed by Sanger sequencing prior to reporting.

1. Joubert syndrome and related disorders (JSRD)

Joubert syndrome and related disorders are a clinically and genetically heterogeneous group of disorders which include COACH, Senior-Loken, Dekaban-Arima and Veradi-Papp syndromes. Inheritance is predominantly autosomal recessive with some rare X-linked cases and the estimated incidence is 1/80,000 to 1/100,000. They are characterised by a distinctive cerebellar and brain stem malformation, the molar tooth sign (MTS), with accompanying hypotonia and developmental delay. Other variable features include retinal dystrophy, hepatic and renal abnormalities.

JSRD are caused by mutations in genes encoding proteins of the primary cilium or centrosome. The Joubert NGS panel includes all 18 genes currently known to be associated with JSRD. Estimated clinical sensitivity is ~50%; as not all causative genes are known. MLPA analysis is also undertaken for NPHP1 (as 95% of mutations in this gene are homozygous deletions) and is included in the cost.

Referrals are accepted from Clinical Geneticists for patients who have Molar Tooth sign on MRI plus at least one of the following; eye movement disorder, abnormal breathing pattern, hypotonia evolving into ataxia and/or developmental delay. We aim to report routine diagnostic tests within 80 days and the cost of the Joubert NGS panel is £900.

For more information on the Joubert syndrome and related disorders service please see our website (www.ouh.nhs.uk/geneticslab) or use the contacts below.

Laboratory Contact
Dr Penny Clouston Tel: 01865 225592
penny.clouston@ouh.nhs.uk

Clinical Lead
Dr Andrea Nemeth Tel: 01865 226010
andrea.nemeth@ndcn.ox.ac.uk

2. Inherited ataxias

The inherited ataxias are a highly heterogeneous group of neurological disorders which affect individuals of all age ranges. The most common ataxias are caused by trinucleotide repeat expansions, including spinocerebellar ataxias 1, 2, 3, 6, 7, 17 and Friedreich ataxia, however, causal point mutations have also been described in a wide variety of other genes.

As clinical phenotypes are often non-specific, screening by next generation sequencing provides an efficient method for interrogating heterogeneous patients without a molecular diagnosis. The Inherited Ataxia NGS panel includes 43 genes currently known to be associated with ataxia. Newly identified ataxia genes will be added to the NGS panel as they are reported in the literature.

Referrals are accepted from Clinical Geneticists, Neurologists and Paediatric Neurologists for patients who have had the standard testing for spinocerebellar ataxias 1-3, 6, 7, 17 and Friedreich ataxia. We aim to report routine diagnostic tests within 80 days and the cost of the Ataxia NGS panel is £1020.

For more information on the Inherited Ataxia service please see our website (www.ouh.nhs.uk/geneticslab) or use the contacts below.

Laboratory Contact
Dr Penny Clouston Tel: 01865 225592
penny.clouston@ouh.nhs.uk

Clinical Lead
Dr Andrea Nemeth Tel: 01865 226010
andrea.nemeth@ndcn.ox.ac.uk

ACGS News Editor

Deadline for contributions for next issue is 30 November 2013

Molecular Genetics Editor -
Dr Martin J Schwarz PhD FRCPath

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Editorial

In addition to reading this AGNC section, please don't miss the article by Judy Tocher from the GC Training Panel on concerns about the future training of Genetic Counsellors at the beginning of this BSGM Newsletter. This is a time of considerable change for genetic counselling, both in terms of future training and in how we are regulated; and Diana Scotcher discusses this in her article on behalf of the Genetic Counsellor Registration Board (GCRB) in which she explains about the Assured Voluntary Register (AVR). Meanwhile the challenges of whether to report incidental findings in clinical exome and genome sequencing are addressed in the AGNC article. There is a link to the position statement from the National Society of Genetic Counsellors (NSGC) in the USA which expresses concern about the potential for patient's loss of choice.

The Manchester GC team and their department are highlighted in this issue with a helpful summary of who they are and how they work. And we have feedback on the successful spring meeting in Durham, a workshop for Duchenne muscular dystrophy carriers and what it's like to present at the BSHG conference. Many congratulations to Professor Maggie Kirk for being made a fellow of the Royal College of Nursing.

Lastly you will see that Registered GCs are now encouraged to use their registration number on all correspondence. I will now practice what I preach.

Vicki Wiles, Cambridge
Principal GC and Registered Genetic Counsellor No: 148

Genetic Counsellor Registration Board (GCRB) update

Diana Scotcher, Deputy Chair GCRB

AGM at AGNC Spring Meeting, Durham, 16 April 2013

Barbara Stayner gave the Chair's report on aspects of the year's work, many of which have been reported in previous newsletters. In January 2013 the GCRB identified two key priorities, the first of which was to improve financial stability. Although we are breaking even financially, there are challenges ahead which will stretch our situation. In practical terms, this will mean changes to the frequency of renewal fees, and developing a new business plan to ensure we can meet financial challenges of the future. The second key aim is to increase transparency with patients and the public. One key task will be to redesign the GCRB website with the aim of communicating GCRB processes clearly to members of the public who wish to learn about the profession and/or make a complaint.

Assured Voluntary Register (AVR)

An important issue presented at the AGM was AVR. With the route to the Health and Care Professions Council (HCPC) firmly closed, the only way to achieve professional regulation is to apply for AVR with the Professional Standards Authority (PSA) (http://www.professionalstandards.org.uk/). The AVR accredits Voluntary Regulatory bodies that are regulated on a voluntary basis. After some considerable thought and discussion, the GCRB now firmly believes that AVR will be good for patients, good for the GCRB and good for genetic counsellors. The GCRB have met with the Joint Committee on Genetic Counsellor Regulation (JCGCR) to discuss the best way of making this happen.

With assistance from JCGCR, the GCRB will need to make an application, demonstrating how we meet the expected AVR standard. This has a number of elements, all of which must be demonstrated through evidence presented in a portfolio:

- governance
- setting standards for registrants
- education and training
- managing the register
- engaging with the public

One opportunity will be to present the risks of our profession to the regulatory body. There are two possible outcomes from the AVR application.

1. If the PSA felt that AVR was not sufficient regulation for our profession they may approach the government on our behalf to suggest statutory regulation. The JCGCR have audited risks from GC clinical leads and this will form part of our application for AVR.

2. Alternatively, a successful outcome from our application would be that GCRB is accepted onto the AVR register. In this case GCRB processes will have been judged sufficient for continued self regulation, the profile of Registered Genetic Counsellors will be raised, the profession will be judged to have met expected standards. However, the title of Genetic Counsellor will not be protected.

Unlike statutory regulation with HCPC, AVR will be self-funding without support from the government. In this way, the Register must incur the costs of the regulation process. At the current time, the PSA has set a fee of £12,000 for application process, and £9,000 per year to remain on the AVR register. This is an important consideration, and means that we will need to review our financial situation. The GCRB will need to demonstrate it is financially robust. This will involve realistic salary costs for an administrator and changes to the website and fitness to practice procedures. The total cost of AVR and the opportunities to raise funds will be known over the coming months. In relation to this

'The GCRB urges all Registered Genetic Counsellors to start using their GCRB number on correspondence as soon as possible'

and the current GCRB work, we have decided that renewal fees will be annual from 2014, and are likely to increase in order to improve financial stability.

As a profession, we need to decide when is the best time for the GCRB to apply for accreditation by the AVR. Registered Genetic Counsellors must be prepared to take part in an online vote, which is likely to take place towards the latter part of this year. In the meantime a JCGCR YouTube video explaining importance of AVR for genetic counsellors will be distributed to AGNC members, patient groups, MDT colleague groups, BSGM and other interested parties. The GCRB urges genetic counsellors to discuss this important issue with colleagues and ensure that all relevant professionals are fully informed of the issues.

Changes to signatures for all Registered Genetic Counsellors

A valuable way of raising public awareness of the role of the Registered Genetic Counsellor is by adding GCRB with a registration number to signatures on all letters and case notes. Many of our medical colleagues already do this, putting the GMC number at the end of correspondence. There has been some discussion about the best way of implementing this and each department may have to decide as a group what suits them. Suggested signatures are:

Jane Simpson
Genetic Counsellor GCRB Registered 544

Jane Simpson, BN, PhD
Consultant Genetic Counsellor (GCRB Registered 727)

Jane Simpson, RN, RGC
Genetic Counsellor
GCRB Registered 38/NMC number 2153

At the moment some genetic counsellors are not registered with GCRB. Nurses who have maintained nursing registration may choose to put a NMC number after their name, and genetic counsellors who have an MSc in Genetic Counselling may add this qualification.

It has also been suggested that the general public may not know what GCRB stands for, so the addition may mean nothing. This is a challenge to address over the forthcoming years. Ideas have included adding information about the GCRB to departmental leaflets and websites.

The GCRB urges all Registered Genetic Counsellors to start using their GCRB number on correspondence as soon as possible.

Current GCRB roles

Barbara Stayner (Chair)
Diana Scotcher (Deputy Chair)
Diane Stirling (Company Secretary)
Catherine Watt (Treasurer)
Caroline Benjamin (Secretary, Sign-Off Mentor training)
Sally Watts (Sign-Off Mentor Training)
Jennifer Wiggins (Overseas/Reciprocity)
Marion McAllister (Academic Associate)
Lorna McLeish
Dr Melita Irving (Medical Associate, Clinical Genetics, Guy's Hospital)
Melissa Hillier (Lay Associate, Genetic Alliance UK)
Chris Barnes (Administrator)

The GCRB administrator

Chris Barnes does an efficient job as our administrator, and we would like to thank her for the time and effort that she puts into supporting the GCRB. Chris works part time and we know she attends to all questions as promptly as possible, and may also have to liaise with a board member. Chris can be contacted at cabarnes@blueyonder.co.uk

AGNC report spring summer 2013

Carolyn Owen AGNC Chair

The AGNC are working closely in partnership with the GCRB, JCGCR, GCTP & Lead GC Group.

The key targets for the AGNC Committee for 2013/14 are:

- Standardising / Best practice
- Regulation
- Website
- Commissioning
- Conferences

Clinical Reference Groups (CRG) developments are well under way with Professor Frances Flinter at the helm. The role of the CRG is to advise commissioners on commissioning issues relating to England. Oonagh Claber is the named person representing the AGNC. PGD specification will be a key issue for 2014 and Alison Lashwood, Guy's and St Thomas's London will be heavily involved. Recording laboratory activity will be another issue being considered. Any members who wish to bring comments to this group should contact Oonagh Claber at Oonagh.Claber@nuth.nhs.uk

Genetic Counsellor Training Panel (GCTP). Judy Tocher is Chair of the training panel. The Department of Health (DH) 50% funded scheme is drawing to a close with the final four trainees due to complete in 2013. A simplified version of the paper work is currently being trialled by one centre.

The GCTP continue to explore ways in which funding may be secured for future trainees, however there is an acute awareness of the challenges faced in the current climate and culture of the NHS. Meanwhile, the GCTP are keen to encourage centres to revalidate as a training centre and to establish their own band six training posts. Request for monitoring by the GCTP with the intention of supporting both trainees and the training centres are welcomed to continue with the successful model established by the DH training scheme and to ensure the future of high quality training for genetic counsellors.

Workforce issues has remained high on genetic counsellor's agendas this year. The AGNC plan to produce a workforce planning report from data collected from the lead GC group (2012) which will be shared with the membership through the AGNC website. Members are encouraged to feed their questions, projects and developments to the committee.

The AGNC are also considering reviewing the multidisciplinary team working in genetics document which is due for review 2014. Comments from the membership are welcomed.

Retiring genetic counsellors 2012 – 2013. A number of experienced genetic counsellors have retired in the past year. We wish them all a happy and fulfilling retirement and thank them for their significant contributions.

They include:
Lauren Kerzin-Storrar – Manchester (2012)
Marion McJanet – Aberdeen (October 2012)
Rose Cullen – Birmingham (2013)
Fiona Robson – Leeds (October 2012)
Linda Rae – Leeds (March 2013)
Sue Wild – Leeds (March 2013).

Spring Meeting Update
3 April 2014 - Bristol

Spring 2015 – Merged meeting with the ESHG – this was agreed at the AGNC AGM by majority vote. The BSGM scientific programme committee are working hard to incorporate psychosocial elements into the programme to encourage genetic counsellor attendance. It is hoped that both AGNC and GCRB will hold their AGMs at this meeting also. There are numerous developments within the ESHG towards European registration for genetic counsellors and nurses and as many of our community are involved with the ESHG it will be an excellent opportunity to show our support.

2016 (2day) - Liverpool.

Exome sequencing in the clinic. A working group has been organised on behalf of the AGNC led by Anna Middleton. The purpose of this group is to represent the membership on issues relating to the patient's 'right not to know'. It is planned that the AGNC will produce a separate response and a joint report with the BSGM. The ESHG also plan to produce a piece of work which has been postponed until after the ESGH meeting in June. The US equivalent of the AGNC The National Society of Genetic Counselors has already produced a press release (http://bit.ly/Yffz7n). Any contributions or comments please contact either Anita Bruce at anita.bruce@nhs.net or Anna Middleton at am33@sanger.ac.uk.

New Developments and Changes

Liwsi Kim Protheroe-Davies – AGNC Webmaster and Committee Member.

AGNC Committee Update

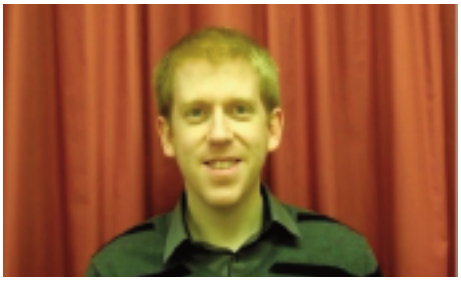
Current committee 2013

‘The GCTP (Genetic Counsellor Training Panel) continue to explore ways in which funding may be secured for future trainees, however there is an acute awareness of the challenges faced in the current climate and culture of the NHS’

As of September 2013 our current chair Carolyn Owen (Wrexham) will step down and leave the committee after six years and the new chair will be Laura Boyes (Birmingham). Carolyn will be sadly missed. She has taken an energised and professional approach to her role on the committee and as chairperson and added her own unique sprinkle of fun to the proceedings! The very best of luck to you Carolyn, for whatever your future holds.

There will also be some other changes with Anita Bruce (GOSH) leaving her post as secretary and becoming Vice Chair as Oonagh Claber (Newcastle) is stepping down from this position but will continue as a committee member. Next year Cath King (Bath and Bristol) will be stepping down as treasurer and Liwsi Kim Protheroe-Davies (Swansea) is due to take over in addition to her webmaster role.

We will also be welcoming a new committee member from September: Peter Marks from Birmingham.



In addition we have a new representative for the New/Trainee group: Claire Giffney also from Birmingham, who will be taking over from Sarah Wilcox (Cambridge). Sarah has now become an ‘oldie’ like the rest of us – good luck Sarah for the future and thank you for your contribution to the committee.

Chair Laura Boyes, Birmingham, West Midlands

Vice Chair Anita Bruce GOSH, London
Treasurer Liwsi Kim Protheroe-Davies Swansea
Secretary TBC

Oonagh Claber Newcastle
Cath King Bath
Donna McBride Southampton
New Committee Member - Peter Marks, Birmingham, West Midlands
New/Trainee Group Representative - Claire Giffney, Birmingham, West Midlands

New AGNC Website. As part of the redevelopment of the BSGM website the AGNC website is NOW LIVE. We welcome any suggestions or comments about the new website and are continually working on developing the content and meeting the needs of our membership. Some of the areas on the website are linked to the BSGM site and controlled by their webmaster e.g. jobs, conferences. The new site also includes a members’ only section only available through your individual log in and we would like to hear from you with regards to what you think should be included in this restricted access area. Please contact the webmaster with any thoughts Liwsi.protheroe-davies@wales.nhs.uk.

The AGNC committee would like to take this opportunity to thank Anita Bruce for her sterling work over the last few years in maintaining and updating our old website. Her considerable contribution is greatly appreciated, particularly given the complex and frustrating technology that was available to run the old website. This role was undertaken, as are all roles on the committee, on a voluntary basis and on top of a very busy case load and therefore many hours and late nights were par for the course. Thank you very much Anita and good luck with your remaining time as the AGNC secretary and onwards as vice chair.

New Logo?

Association of Genetic Nurses and Counsellors

At the recent AGNC Spring Meeting Carolyn Owen presented the idea of updating our logo. Members are invited to design a ‘new’ logo. We have already received some designs and are encouraged by the response of our membership. If members have any further suggestions or ideas and wish to display their creative abilities please contact Anita Bruce AGNC secretary - anita.bruce@nhs.net

The committee would like to thank Oonagh Claber and her organising committee for arranging such a diverse and thoroughly enjoyable spring meeting.

Notes from a Spring Meeting

Oonagh Claber, Newcastle (spring meeting organising committee)

"Why, it's a perfect little city. If you have never been to Durham, go there at once. Take my car. It's wonderful." – Bill Bryson

The AGNC spring conference 2013 was held at Durham University's Collingwood College on the 15 and 16 April was a resounding success and I feel it was probably worth the stress levels it induced in me in the prior months.

As well as varied presentations from the membership there were talks from the Newcastle neuromuscular genetics service and the Newcastle mitochondrial service.

On Monday afternoon we held a mini symposium on antenatal diagnosis of cleft lip and palate with detailed 3D ultrasound images and a very moving account from a mother whose baby was diagnosed with a cleft antenatally.

On Tuesday there was a session on new technologies in genetics and the difficulties with the interpretation of results. Professor Sir John Burn also entertained us in his inimitable fashion with his whistle-stop tour of the future.

The poster prize was won by Tara O Neill from Belfast with her poster Offering a choice for cancer predictive test results.

This year as well as the AGNC AGM, the Genetic Counsellor Registration Board (GCRB) AGM also took place allowing a greater number of members to attend the latter than in the past, and this is something we aim to continue.

The conference dinner was held in the grand setting of Durham Town Hall. The after dinner disco was a hit; so much so that the enthusiastic dancing of one of the organising committee ended up causing her a hip injury requiring a trip to A & E the following day. Fortunately no lasting damage prevails and she lives to boogie another day.

A profile of Genetic Medicine in Manchester

Ruth Kirby, Genetic Counsellor Manchester

Manchester's genetic counselling service sits within the Genetic Medicine directorate, integrating clinical genetics with molecular genetic and cytogenetic diagnostics and research. In 2009 the clinical and laboratory services merged with the Willink Biochemical Genetics Unit for paediatric metabolic medicine, to form one of the largest genetics directorates in Europe, serving a population of around five million. Along with academic programmes in molecular genetics, health services research, and the MSc Genetic Counselling Programme, we are also closely associated with the Manchester Biomedical Research Centre and Nowgen – A Centre for Genetics in Healthcare.

Our service is provided from the regional hub at St Mary's Hospital, a new, purpose-built centre with 5,000m2 of integrated clinical and laboratory space and from clinics throughout the north west of England.

Sixteen WTE consultant/honorary consultant clinical geneticists and seven SpRs/STs, cover dysmorphology, prenatal, neuromuscular, neuropsychiatric, ophthalmic, cardiac, renal and cancer genetics, deafness and cleft palate clinics. Also in the clinical team are two consultant neurologists, and the biochemical genetic staff comprising six consultant paediatricians, paediatric SpRs, nurses and dieticians. Genetic Medicine includes three nationally commissioned services: for complex NF1, NF2 and lysosomal storage disorders.

The team of genetic counsellors (17.6 WTE) includes three consultant genetic counsellors Tara Clancy, Rhona MacLeod, and Georgina Hall, three principal GCs Alison Clarke, Diana Scotcher and Catherine Houghton. The GC team cover both cancer and general referrals, and some have developed specialist areas. All GCs cover urgent referrals on a one-week rota basis. The majority of the GCs are registered, and the remainder are working towards registration, supported by six trained registration mentors/assessors within the team.

Since the Department of Health trainee programme began in 2003, ten genetic counsellors have successfully completed their training posts in Manchester. As well as mentoring, most of the GCs are regularly involved in supervising students on first and second year placements as part of the MSc programme in genetic counselling in Manchester.

Departmental seminars are held weekly, often with external speakers. Following a weekly GC meeting, we have a clinical meeting with the whole team, which includes updates from the cytogenetics and molecular labs, discussion of urgency cases, ward referrals, and usually a presentation.

Genetic counselling is provided both independently and as part of consultant-led clinics. In response to increasing referral rates and in common with many other genetics services around the country, we tend not to carry out home visits except in particular circumstances. In the last few years, we have largely stopped pre-clinic work-ups and we now bring most patients straight to clinic. In the case of cancer referrals, we seek confirmation of diagnoses

Feel the fear and do it anyway: Experiences of a new genetic counsellor

Anna Beach, Manchester

following the first clinic visit and, depending on the scenario, follow up with the patient by letter, phone or further clinic appointments.

Since 1989, we have run a genetic register service to manage families proactively, for example in terms of screening and research. The service has grown to cover many specific genes/conditions, including BRCA1/2, Lynch syndrome, FAP, VHL, MEN, Gorlin syndrome HD, DMD, BMD, Fragile X, and Myotonic dystrophy. More than 3000 families have opted to join the register. Most of the genetic counsellors have responsibility for some register work, which involves an annual review of each register file, and contact with patients and family members where appropriate. Through the register we are well placed to respond to advances such as the development of genetic based therapies.

As a genetic counsellor freshly emerged from the MSc course the opportunity to submit an abstract to the British Society of Human Genetics Conference (BSHG) was a relatively abstract exercise (excuse the pun) without a true understanding of what that entails or whether it would be accepted. The abstract outlined the research project I'd undertaken as part of my MSc in Genetic Counselling; exploring the impact of pre-symptomatic genetic testing for BRCA1 in young people, aged 18-25 years. I thoroughly enjoyed the research process and would be tempted to write more about my findings here however I will save that for another day.

To my surprise, and delight, the abstract was accepted for a spoken presentation at the BSHG, it wasn't long however until I realised that I'd have to present at the BSHG.

As prepared as I could be I wanted to make the most of the opportunity to attend the conference. The opening speakers were faced with the challenge of presenting what they thought the future of Genetic Medicine would look like. As a genetic counsellor very new to the profession and despite the nerves associated with the looming presentation, I was left feeling very motivated by the speakers. It also made me reflect on where I saw genetic counselling. A theme that seemed to crop up in this and later sessions was the demand, and need for genetic testing to be more accessible for clinicians in other specialties. This is only likely to increase as over time ever more genetic tests will be available; too many for a single specialty to oversee.

Luckily I was scheduled to present on the first afternoon so once that experience was dispatched with, I was fully able to continue to enjoy my first experience of a large national conference. The wide range of speakers, too numerous to mention provided many new insights and inspiration for me. The Education session regarding the educational role of genetics specialists again highlighted that a time is likely to come when non-genetics specialists will be directly accessing many more genetic tests than is currently the practice. This to me seemed to highlight that genetics professionals are valuable resources who need to assist in the education of non-genetic specialists who will be responding to changes in technology and clinical service provision. The march towards 'direct to consumer testing' seems inevitable, and in fact already offered (via Google).

Whilst there is often an impression in the public arena that the more research is carried out into genetic diseases the more we know, in fact clinicians seem all too aware that often the more we find out the more we realise we don't know. Exome sequencing at one time promised many of the answers however the importance of the 'regulome' (formerly known as junk) is now all too apparent. The role of genetic counsellors in translating this information into a clinical setting seems even more valuable (although I would say that). Helping patients to understand, assimilate and adjust to incomplete and uncertain information will be increasingly important.

Whilst the genomic revolution rolls forward, combining with all the other 'omics' yet to come, I find it fascinating, and at times intimidating to imagine the changes that will come about during my career as a genetic counsellor. The importance of rising to meet the challenges seems to be highlighted once again through the recent publication by

I'm a carrier: What do I do now? A session for parents and older siblings

Anita Matadeen, Genetic Counsellor, St George's London

the American College of Medical Genetics and Genomics (ACMG) regarding their position on the reporting of incidental findings.

Reflecting both after the BSHG and following the recent ACMG position paper I am left with a mixture of feeling overwhelmed with the task facing the genomic medicine community and excited and proud to be part of it.

I would encourage any new genetic counsellors who are considering submitting an abstract to a conference to do it. Despite my nerves it was apparent that the audience were supportive and encouraging. I'd especially like to thank Rhona MacLeod for all her help and support throughout the process of conducting and presenting my research. Also thanks to the AGNC in supporting me to attend and present at the conference. Finally I hope to see you all at the first British Society of Genetic Medicine conference.

Sue Kenwrick (Principal Genetic Counsellor, Cambridge) and I held this workshop at the Action Duchenne International Conference in November 2012. In planning for the workshop, we were unsure of what topics our attendees might want to discuss. As we were also wary of leading the discussion too closely, a collection of slides covering a range of topics were developed to supplement any emerging topics.

As a number of interesting talks were presented simultaneously, a large turnout was not anticipated. Approximately 20 people participated and most participants were women representative of all age groups. Some male partners also attended although no teenagers were present. The workshop opened with a general discussion about genetic counselling and the genetics of Duchenne and Becker muscular dystrophy (DMD and BMD), followed by small group discussion and feedback which set the tone for the remainder of the workshop.

Several issues emerged including a repeated concern regarding recognition of symptoms related to being a manifesting carrier. One carrier described being very flexible and consequently overtly worried about her own health and the effect that this might have on how she would maintain caring for her children. Another carrier described feeling short of breath and worrying about whether this could be indicative of related cardiac abnormalities. Also discussed was the nationwide variability in cardiac screening recommendations for manifesting carriers which suggests an area for further attention in future research and perhaps further discussion among professional groups.

Furthermore, the workshop seemed also to have functioned as a resource for gaining peer support as evidenced by some carriers who chose to continue their discussion after the workshop had closed. These carriers felt that a peer support group, perhaps similar to the workshop setup, would be helpful so that concerns and experiences could be shared among carriers. This included how and when to discuss carrier testing with daughters, 'sharing the load' of caring for affected sons, and family impact of illness. It also emerged that although some areas in the country had access to support workers, other areas had none. The Muscular Dystrophy Campaign has a small number of support groups which may be helpful to some carriers.

The workshop provided a unique insight into the concerns of female BMD/DMD carriers. We felt that it was important to share some of these concerns with our colleagues who might also find this helpful in the genetic counselling consultation. We have been asked to return next year and we hope that this will aid in forging greater links with the BMD/DMD community.

AGNC member awarded FRCN

AGNC member Maggie Kirk has been awarded a Fellowship of the Royal College of Nursing (FRCN) in recognition of her "outstanding contribution to the art and science of nursing" in the field of genetics education. The FRCN is the highest honour the RCN can award and this is through peer nomination only.

Maggie spent the first nine years of her postgraduate career as a mammalian geneticist, leaving the MRC genetics unit at Harwell in 1985 to become a nurse. She moved into nursing education and research in 1992, joining the Genomics Policy Unit, University of Glamorgan in 1996, to explore the implications of advances in new genetic technologies for health professionals. She was conferred with a personal Chair as Professor of Genetics Education in 2004 and from 2004-2012, took on an additional role as Lead Professional Specialist (Nursing) at the NHS National Genetics Education & Development Centre. In 2006 she was awarded the Founder's Award for Education by the International Society of Nurses in Genetics, of which she is also now President-Elect. She has been an AGNC member for nearly 20 years.

Maggie said "I am fortunate in that the excellent people I collaborate with, in the Genomics Policy Unit at the University of South Wales and further afield, share my passion for trying to improve the healthcare experience of individuals and families affected by inherited conditions, through encouraging nurses and other health professionals to engage with genetics."

AGNC News Editor

Deadline for contributions for next issue is 30 November 2013

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Editorial

Natalie Canham, KGC

So, the big bang of NHS commissioning so far appears to be a bit of a damp squib from the genetics point of view, largely because the important thoughts about what should happen were only thought late in the day. However, the Medical Genetics Clinical Reference Group, chaired by Frances Flinter, has worked very hard on a useful service specification, and hopefully the plans about mainstreaming and funding of laboratories will benefit from the year's grace period introduced at the last minute.

The CRG has been disbanded and reformed, with some new faces (including my own) and some old. Most, though not all are from the genetics community, and we all seemed very well behaved at our recent teleconference, which is an experience in itself if you have not previously participated in one. CRGs are described as "the primary source of clinical advice to NHS England in support of the direct commissioning of prescribed specialised services", which is slightly intimidating, but it is good to know that we in the genetics world are being consulted about what our job should actually be.

Another successful CGS conference has occurred, and the associated dysmorphology meeting. I find it very gratifying that we have more and more people from overseas participating in this meeting – I think this represents the recognition that we have some true experts in the field in our country, and also reflects the fact that collaboration so often improves genetics knowledge. I think we are a very cohesive and supportive community, and this has to be an advantage as we move into the brave new world of national commissioning, mainstreaming and competition. It has to be hoped that the last aspect particularly will not worsen relations between departments and individuals. Genetics as a whole will be stronger if we pull together rather than pull apart. I think that this applies both between the laboratory and clinical teams, and also within the discipline as a whole.

We now have a new president of CGS, and Jill has made some very interesting comments in her letter. I am of course grateful for the kind sentiments about the newsletter itself, and would of course join her in recommending that you download it onto your tablet (if you are such a technologically blessed person). I would, as usual, also request that people send me articles – an unsolicited entry really makes my day, as I seem to spend all social occasions attempting to induce people to write for me. I would, of course, much rather not bother you all at all times

Letter from the president

Jill Clayton-Smith, Manchester

I recently found myself in the anxious position of having to write a contribution to the CGS newsletter in my new role as President of the Clinical Genetics Society. Knowing that I'd never be able to emulate Peter Turnpenny's erudite prose, I looked back through past BSHG newsletters to seek inspiration. Several hours later, I was much more knowledgeable on a wide range of topics from the history of genetics to designing clinical trials, and the first thing I would say is that these newsletters really are enlightening, even better the second time around. I would recommend that you download them onto your tablets for train journeys right now.

Peter's last newsletter sought to reassure us all that Clinical Genetics is not a dying specialty and this has been reinforced to me on an almost daily basis over the past few weeks. At the stimulating CGS Spring Conference in April there were many examples of the type of work we will undertake increasingly in the future. The massive leaps forward in gene identification through exome sequencing have brought with them greater understanding of the aetiology of genetic disorders and greater possibilities for treatments. The examples of progress in Alport syndrome and renal angiomyolipoma are surely a taste of things to come, when clinical geneticists will be refreshing their prescribing skills and once more reaching for their prescription pads. Some will take the advice of Diana Eccles who described the route to becoming a clinical trialist in the last newsletter. I recently discovered the joys of clinical trials during our involvement in a Fragile X pharmaceutical trial. I can vouch for the fact that anyone undertaking to be a PI for such a trial might look forward to a huge amount of paperwork and e-learning training packages, many site visits, a very full e-mail box and a return to being contactable at all hours if you hold the

"Yes, we can be reassured that we will have plenty to do in the sequencing era....."

special unblinding information. On the up-side you get to work with terrific clinical trials staff, gain a lot of new knowledge and get that nice warm feeling of being a 'proper doctor' from time to time. Every trainee in particular should try it.

The presentation by Anneke Lucassen at the CGS meeting on incidental findings and their management was of great interest and provoked much discussion. The debate has intensified subsequently with the recent publication entitled Recommendations on Incidental Findings in Clinical Exome and Genome Sequencing, from the American College of Medical Genetics and Genomics. This was drawn up by a Working Group advised by an expert panel, and has caused some consternation on this side of the pond. The authors presented a list of genes, many involved with cancer predisposition and cardiac disorders, in which laboratories were recommended to seek and report genetic variants. These results would be disclosed to patients, both adults and children, with the most contentious issue being that patients undergoing screening would have no choice about whether to receive this information or not, and that exome/genome sequencing would be denied to them if they did not consent to disclosure of these incidental findings. This is somewhat at odds with current thinking within the United Kingdom. The Public Health Genetic Foundation published a statement on their website expressing their 'dismay', and suggesting that such a guideline may have been driven in part by medico-legal issues. Others will disagree with the statement that "fiduciary duty supersedes autonomy" but will have some sympathy with the wish to act on any clinically useful information obtained through sequencing and this will no doubt be one of the major debates for those involved in the UK 100,000 genome project.

The other issue this publication raised was just how much work and responsibility was expected to be taken on by the clinical geneticist. Roles included undertaking an extremely comprehensive consent procedure, disclosure of results to patients after re-evaluating the clinical and family history and phenotype and checking that they correlated with results, and post-test counselling. The US guideline recommended particular reinforcement that if there were no incidental findings to report back, this did not imply assurance of absence of any pathogenic variant. After all this, the clinicians would then take on the task of organising follow-up with appropriate health surveillance and of course, everything needs documenting carefully, should there be any redress, especially if deviating from the guidelines. Preliminary discussions concerning the UK 100,000 genome project, due to begin in April 2014, also seem likely to confirm a key role for the clinical genetics team in recruitment, interpretation of results as part of a multidisciplinary team , feedback to patients with re-evaluation of clinical phenotype if necessary and organization of follow-up for patients and extended families. Yes, we can be reassured that we will have plenty to do in the sequencing era.....

Looking to our future clinical workforce, it was good to welcome a group of enthusiastic trainees to the recent dysmorphology course in Manchester. Course attendees can apply for scholarships from the ESHG and there was representation from many countries including Italy, Greece, Poland, Spain, Romania, Latvia, the Netherlands and Israel as well as from the UK. Trainees got a chance to exchange their experiences of training in countries with very different systems and circumstances and most will have made contacts who they will keep throughout their future careers. For some, the recent news that the Union of Medical Specialties in Europe (UEMS) will soon establish a Clinical Genetics Section is important news. The UEMS has the remit of harmonising training and education of medical doctors and it is anticipated that the first meeting of the new section could take place at the ESHG meeting in June, attended by two delegates from each country. I anticipate that we will be able to contribute a great deal of our UK experience of training to others. Though there are sceptics, being part of a broader European Genetic Community will surely have some positive influences on our practice. As I write this, the UK Rare Disease Plan is being formulated in response to a European Union Directive and with significant input from patients and patient organisations. The plan is expected to have patient benefit as a core objective and support rare disease research and networks, though it seems unlikely to be accompanied by extra resources.

Finally, one can't mention resources without reference to the newly established Medical Genetics Clinical Reference Group chaired by Frances Flinter. The remit of the UK CRGs is to act as a source of expert advice to NHS England on specialised services. The groups have a broad remit, including developing priorities, quality improvement and developing 'products' such as service specifications. Improving value for money and decommissioning also come under the CRG remit. Much work is to be done by this as yet fledgling group, but one thing worthy of mention is that the group needs to develop an 'innovation portfolio'. They want to know about examples of good practice or innovations which could be shared with others and this could bring financial rewards, so don't be shy, let your regional representative know about your good ideas. In this climate of scarce resources, surely austerity will be the mother of some great inventions and the opportunities are there to bring out your creative side.

An elective spent in genetic medicine

Adam Jackson, The University of Manchester

As a final year medical student, I have recently spent four weeks in the Genetic Medicine department at St Mary's Hospital Manchester. During my time at university, I have learnt only a small amount about the field of genetic medicine. In preclinical years we learnt some basic concepts of Mendelian inheritance, which were to set us up for the rest of our studies. Even from this small taster, I was always keen for more and so opted for student-selected components which all had a strong genetic component. However, it was my elective spent in St Mary's which has inspired me the most.

The majority of my time was spent in clinics, gaining an insight into a vast range of genetic disease. Clinics I attended included general paediatric genetics, cancer genetics, dysmorphology, metabolic medicine and a specialist clinic in neurofibromatosis. The diverse nature of the pathologies I saw in clinics gave me a whole new appreciation for the vast knowledge base required by the doctors and genetic counsellors undertaking the clinics. Attending clinic meetings, I was able to experience the multidisciplinary team input into patient care. Having engaged with some of the genetic scientists who carry out the intricate DNA techniques, I was inspired to read more about the grass-roots science, albeit understanding very little. Reading about the technologies at a geneticist's fingertips has provided me with an understanding of cost. Being merely thirteen when the human genome was sequenced, I have lived under the illusion that DNA sequencing and analysis is an easy and affordable task. Even during problem-based learning seminars as a student, we would suggest genetic testing for the patient in the case without question. Nobody asked us if we thought that genetic testing was feasible, we just had to know that it was possible. Having spent time in the clinic meetings listening to discussions as to whether or not to test a patient, I now understand that DNA tests can cost thousands of pounds and in the rarer cases must be sent away to other countries with a result returning months later.

I have worked on two projects during my elective in genetic medicine. My first project was a case report of four patients concerning the incidence of colobomata in patients with fetal valproate syndrome. Researching this area has taught me about epigenetics and particularly histone deacetylases. My second project was an audit of patients with hereditary haemorrhagic telangiectasia. Guidelines for arterio-venous malformation and pulmonary hypertension screening in these patients have recently been published and we are in the process of auditing current clinical practice against them. These two projects have improved my writing skills, while also giving me an insight as to life as a clinical geneticist undertaking research and keeping up-to-date with the latest literature. I have been greatly inspired by the consultants, registrars and counsellors who acted as my mentors during my stay at St Mary's and hope to return in the future.

Trainee report

Hannah Titheradge, ST5, Birmingham

CGS Spring Meeting

It was lovely to catch up with so many of you at the CGS Spring Meeting in London last month. The standard of registrar presentations in the afternoon was very high and made for a very interesting session. Congratulations to Ellen Thomas for winning the SpR presentation prize.

Funding

There will now be a reduced conference fee for UK trainees wishing to attend the CGS Spring meeting. This will not include the four yearly joint conference held outside the UK. A number of travel bursaries are also available to trainees wishing to attend international meetings and conferences. This is subject to application through CGS.

Social media

There is now a CGS facebook and twitter account. To find these go to: @clingensoc on twitter and www.facebook.com/groups/clingensoc on facebook. This is a closed group so approval will be needed. Once you have joined - start posting or tweeting!! There is guidance on doctors' use of social media on the GMC website.

The CGS website has also been updated. There is a trainee section with a very useful document on trainee inductions.

Short overseas electives

An excellent opportunity has been proposed by CGS and the Specialist Advisory Committee for trainees to spend a period of three weeks in a developing country to study genetics as a short overseas elective. This period will not require an application for out of programme exemption and will not extend CCT. It will be assessed through reflective learning and CBDs. Travel grants will be available by successful application to CGS. There will be more information about this to come.

CGS trainee representatives

Emily Craft has now taken over from Meena Balasubramanian as the second CGS trainee representative. I'm sure we are all grateful to Meena for all her work on our behalf. Please feel free to contact Emily or myself about any trainee issues you would like raised nationally at the CGS council meetings. Our contact details are: hannah.titheradge@bwhct.nhs.uk and emily.craft@uhl-tr.nhs.uk. The next meeting will be held in October 2013.

CGS News Editor

Deadline for contributions for next issue is 30 November 2013

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Editorial

Welcome to the latest edition of the CGG Newsletter. In this edition we have two important and thought provoking articles on topics of increasing importance in genetics healthcare. As the impact of immensely powerful genetic technologies grows year by year, genome-wide analyses and the establishment of genetic testing in mainstream medicine are challenging clinicians and patients with a range of complex technical, logistical and ethical issues.

First, Julian Adlard casts a critical eye over mainstreaming genetics services, that is, the integration of gene testing into mainstream (mostly secondary care) medicine. This is a complex and challenging subject with many vested interests. Given the recent plethora of high level advisory committee meetings and workshops devoted to this subject there is clearly an enormous amount of interest, matched by the degree of concern about the potential impact over the next few years of mainstreaming on specialist (tertiary) genetics healthcare services. As Julian points out, at the moment clinical genetics services identify a tiny fraction of individuals (mostly from high risk families) with a genetic susceptibility to cancer. Modern genomic technologies applied to advancements in our understanding of lower penetrance susceptibility gene variants, as exemplified by recent articles in Nature Genetics from the COGS study (see http://www.nature.com/icogs/) and which we featured in the last edition of this newsletter, may have the potential to transform disease risk stratification and attendant surveillance for some of the major cancers. Also considered are issues such as the likely benefits of providing tests closer to the point of care, in the oncology clinic, and questions concerning adequate familial risk and information provision by non-specialist geneticists, and how this can be tackled.

Second, Anneke Lucassen provides us with a timely and carefully considered opinion on the perils and pitfalls of incidental findings (IFs) identified during genetic tests for hereditary conditions. Timely, in that The American College of Medical Genetics and Genomics (ACMG) recently issued recommendations on the return of IFs from genomic technologies in clinical practice. So, this is another 'hot' subject, indeed it has been for a few years now. With the development and use of genome-wide tests, e.g. exome sequencing and microarrays, and the massive amounts of genomic information they generate, we are forced to confront some complex and challenging issues on reporting, interpreting and communicating IFs, or not, as Anneke intricately explores.

We have an excellent article from Caroline Langman and Chris Jacobs at Guy's Hospital on their BRCA carrier support group for the SE Thames region. At least six years in the making, the group is proving to be a great success, not least because of the very close involvement of 'carrier patients' in its development and administration under the auspices of the Steering Group. Gauging the degree of interest and collating ideas from gene carriers across the region had a great deal to do with the popularity of the first support group meetings in March this year. Caroline and Chris have invested a huge effort to launch this initiative, which also happens to be in line with NICE recommendations and their hospital's patient and public involvement policy. There is much to learn from their experiences, we are very grateful indeed for their contribution.

Last but certainly not least is a contribution from Alison Lashwood, Consultant Genetic Counsellor at the Centre for PGD, also at Guy's Hospital. Some of you may have seen Alison's excellent presentation on PDG at the Winter CGG conference at Guy's a year or two ago. This update on cancer syndromes for which PDG is available provides an excellent summary. With the benefit of having been an established service for about 15 years, they have accumulated a great deal of experience and data, approaching 500 babies born from about 1500 cycles, yielding over 1000 embryo transfers. Alison also considers some of the more nuanced issues specific to later onset, potentially treatable/avoidable conditions, a feature of most cancer syndromes for which HFEA PGD licences have been granted. Alison also offers a helpful commentary on the difficult issue of whether a couple with a hereditary cancer syndrome, such as BRCA1/2, and already having a child with 50% risk of being a carrier, are able to gain funding for PGD. For early onset/incurable conditions, couples with a healthy child are excluded from PDG.

Andrew Cuthbert, CGG News Editor

Mainstreaming cancer genetics – opportunities and challenges

Julian Adlard, Yorkshire Regional Genetics Service, Leeds

Introduction

I was invited to write this article about mainstreaming, as one of relatively few consultants who have already crossed the stream from another speciality into cancer genetics. I worked for eight years 50:50 between clinical oncology and cancer genetics, and recently became full-time in cancer genetics. However, mainstreaming implies that rather than transfer more external personnel into genetics, the provision of service moves out into other specialities. Understanding the knowledge, attitudes, service set-up and workload of other specialities such as surgery and oncology will be important when considering how mainstreaming might work in practice.

Opportunities of mainstreaming

There are over 300,000 new diagnoses of cancer each year in the UK. GPs, secondary care services and patients themselves currently determine who is referred for genetic assessment. Direct genetic testing for cancer syndromes has not generally been available without genetics referral and associated counselling. The current system is only scratching the surface of genetic predisposition. We identify relatively few families with high-penetrance syndromes. There is under-ascertainment of these conditions and little or no genetic testing available for moderately increased susceptibility.

Secondary care specialities such as surgery and oncology have greater resources and more direct contact with cancer patients, from initial diagnosis through to treatment and follow-up. Therefore, there is an opportunity for genetic testing to be offered in secondary care. Oncologists are particularly becoming more familiar with genetics, as somatic mutations within tumours have become targets for new treatments. Other specialities, such as endocrinology are also becoming more involved in management of tumour predisposition syndromes. Mainstreaming offers opportunities to widen access to new tests and link results more directly with management.

Challenges

Currently, most oncologists and surgeons have only a basic knowledge of familial cancer syndromes and genetic risk. Most are aware of BRCA1/2, HNPCC, and FAP, but not of rarer syndromes. Increasing sub-specialisation means a surgeon or oncologist may have more limited knowledge of different tumour sites than in the past. They will usually have good training in breaking bad news, but no training specifically in genetic counselling. Other specialities, surgeons in particular perhaps, tend to be more directive than genetics in terms of counselling. Oncologists are used to dealing with families, but only in terms of the direct impact of the diagnosis in the affected patient. Considering the genetic implications for unaffected relatives does not come naturally to most.

Care will have to be taken not to assume that an increased volume of genetics work can be simply absorbed by other specialities. These specialities do not have the luxury of long appointments, and in what time is available, there is already much to cover including details of the diagnosis, prognosis and management. Increasing complicated treatment has to be planned and delivered; side-effects have to be dealt with, and in-patients reviewed. There has been an increasing tendency for services to reduce, automate, or eliminate routine follow-up once treatment is complete. Therefore, in practice, the time that individual surgeons, oncologists and their teams will have to discuss any more complicated genetic issues may be limited. There are concerns that widening access to genetic testing may reduce the quality of associated counselling, interpretation of any results, and dissemination of information to family members. In the same way that a good surgeon should have time and experience to train and maintain skills, the same applies to good management of patients with familial cancer risks.

Ways forward

The on-going revolution in genetics will continue to provide opportunities and challenges. It is unlikely that genetics services will be expanded to take on all of the additional testing that will become potentially available. Therefore, it is entirely appropriate to consider ways of mainstreaming cancer genetics. There will be colleagues in secondary care who will be interested and excited to take on such additional roles. Potentially, they may be trained and given time to take on specific responsibilities within their departments, whilst supervising other colleagues.

Genetics services must continue to provide education, support and advice. Robust patient information will be required, straightforward testing pathways, and easily interpretable results. Whether testing is offered to all patients with a new diagnosis, or to a subset of patients based on family history and pathological information needs to be considered carefully. Investigations into the practicalities of these processes are already beginning, for example with the Mainstreaming Cancer Genetics Programme (http://mcgprogramme.com/). Most of this discussion has been about extending testing to secondary care, but there will also be potential further debates to be had about primary care access, and direct to consumer testing.

Return of incidental findings from genome technologies

Anneke Lucassen
Professor of Clinical Genetics Southampton; Clinical Ethics and Law, Faculty of Medicine, Southampton

The American College of Medical Genetics and Genomics (ACMG) recently issued recommendations on the return of incidental findings from genomic technologies in clinical practice.[1] Reaction to this from some quarters - including the UK's Foundation for Genomics and Population Health (PHG Foundation)[2] - was strong, arguing that these recommendations undermined patients' autonomy, denied their 'right not to know' and transgressed well established guidance on genetic testing of children for adult onset conditions.[3] In response to some of these concerns the ACMG offered 'a clarification',[4] but opinion remains that patients would be "obliged to accept" the results of genomic analysis whether or not they were related to the clinical indication for the test.[5] Genomes unzipped, in their article 'no choice for you', used a case history to emphasise the potential problems resulting from the recommendations.[6] These are of course important issues that require careful consideration, and the BSGM and ESHG will likely reflect on whether the European consensus approach should be similar, and if not, why not.

My view is that the ACMG offer a useful starting point for management of incidental findings from new genomic technologies, which will, as they point out, have to evolve in the light of evidence. Commentators seem to have interpreted the recommendations as requiring forced disclosure of results to patients who do not want them. But I read these as recommendations about laboratory reporting to the clinician, not about what must be disclosed to a patient. Guidelines can be very useful, but they are not meant as absolute rules . As a clinician I must consider the welfare of my patient, and if I am not convinced that this is served by disclosing, for example, a result of uncertain pathogenicity unrelated to the clinical problems, then these recommendations do not compel me to do so. This might need careful discussion, perhaps with other colleagues,[7] but my role has to be more nuanced than simply a conduit of laboratory information.

A full blood count, or liver function test might reveal abnormalities not suspected from the clinical reason for the test, and we do not expect these to be filtered by the laboratory to save the clinician from being 'forced to' disclose unsuspected findings to their patient. Conversely, were I to discover, for example, that a patient being investigated for inherited heart problems has a high risk of bowel cancer, then my duty to disclose (to enable him to access preventative treatments) might outweigh any abstract wishes he had expressed at the time of testing. This is not least because it is difficult, if not impossible, to consent to not knowing the unknown.

In my experience it is rare for patients, or parents, to ask for their results to be limited to ones that are purely related to their clinical question. Furthermore, preliminary results from an on-going qualitative research study in Southampton suggest that new genomic technologies are generally described to patients as "more detailed analyses" or "better tests" with cursory, if any, mention of the possibility of incidental findings. There is no detailed exploration of whether and when they would want to exert their putative "right not to know" any results.[8] Patients do not ask for their results to be limited to certain clinical aspects, but if they did, careful consideration might need to be made as to whether targeted genetic testing of particular genes would be better than genomic analysis.

That's not to say that we should shut down debate about the ethical issues involved as genomics enters mainstream practice. Just because a genomic test may be one of many tests sent off routinely without adequate time to discuss and debate feedback preferences, it does not follow that the ethical issues that have exercised geneticists will disappear. For example, there is widespread consensus that predicting adult onset genetic disorders is generally best left until a person is old enough to decide for themselves.[9] Disclosure of BRCA 1 or 2 mutations may not be in a child's best interest aged two, but adult relations may have an interest so that they can be tested at a time when interventions are available. How do we manage this tension? 'Carrier' results may be very relevant to inform reproductive choice but NHS systems are not set up to manage delayed disclosure of results. What about variants of uncertain pathogenicity when the consequences for the patient are not clear; should we disclose these? Again

[1] A finding that is incidental to the clinical reason for doing the test, also termed 'secondary', 'non-pertinent' or 'unexpected' findings.

[2] As the recommendations state: "This guideline is designed primarily as an educational resource for […] health care providers to help them provide quality medical genetic services. Adherence to this guideline does not necessarily assure a successful medical outcome. This guideline should not be considered inclusive of all proper procedures […]In determining the propriety of any specific procedure […], the geneticists should apply his or her own professional judgment to the specific clinical circumstances …

‘…were I to discover, for example, that a patient being investigated for inherited heart problems has a high risk of bowel cancer, then my duty to disclose […] might outweigh any abstract wishes he had expressed at the time of testing.’

experience from clinical practice suggests that non-disclosure is often not a realistic option: A variant might best be traced through a family in order to determine its pathogenicity through linking it with presence or absence of clinical features and this can hardly be done without some disclosure. The familial aspects of genetics with the attendant (occasional) tensions for individual consent and confidentiality will continue to challenge us in the era of personalised genomics.

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Setting up a BRCA support group at Guy's: a patient/professional partnership

Caroline Langman and Chris Jacobs, London Guy's Hospital Genetic Centre

The BRCA Family Service at Guy's Hospital has been established within Guy's Regional Genetics service since 2006, providing a one-stop multidisciplinary clinic, on-going follow up, regular information updates and support for BRCA carriers. One of the most frequent requests made by BRCA carriers attending this service has been for an opportunity to meet with other carriers. Providing peer support is also a requirement of the NICE guidelines for Familial Breast Cancer. At Guy's we have tried several ways of providing this peer support, including a lunchtime support group facilitated by a clinical psychologist on the day of the clinic (this is/was not well attended); support groups at the six monthly patient update meetings (these are well attended and with positive feedback but not frequent enough); and a 'Welcome and Genetics Research Information' talk for all patients attending on the day of the clinic. The original aim of the research talk was to provide patients with information about on-going relevant research in order to increase recruitment and provide an opportunity to meet others in a group environment. It quickly became clear that there was an unmet need to share experiences. Caroline Langman, the Senior Research Nurse who was running these sessions, identified a training need and embarked on the 12 month examined Macmillan Cancer Support course to learn how to facilitate support groups. However, we found that there was insufficient time during these sessions to provide really helpful peer support.

At about this time, we were approached by one of our patients who was keen to set up a patient support group and wanted our help with this. After careful consideration and discussion, we decided to explore the possibility of setting up a group in partnership with our patients. By this time Caroline had completed her training and was keen to take this forward. In line with the Trust Patient and Public Involvement (PPI) policy, we first set up a Steering Group consisting of BRCA carriers and genetics clinicians (Caroline Langman and Chris Jacobs) to identify the aims of the support groups and when, where and how these should be run. We invited BRCA carriers who expressed a desire to help, in whatever way, that they could. They would bring a variety of perspectives to the group. The resulting Steering Group consists of an enthusiastic mixture of people, some with and some without cancer, and from a variety of backgrounds including a beautician, a social worker and the wife of a GP.

The Steering Group has met three times in the last nine months. They have agreed the name and Terms of Reference of the group, how the support groups should run, as well as reading and commenting on patient information leaflets and research proposals relating to BRCA carriers. The Steering Group were very keen that the support group should be run and administered under the umbrella of the BRCA Family Service. Currently, the Steering Group is chaired by Chris, the support groups are facilitated by Caroline and attended by at least one 'patient' Steering Group member. However, the aim is that patients will eventually undertake training to chair the Steering Group and facilitate the support groups.

A letter, drafted and signed by the Steering Group, was sent out via the BRCA Family Service to BRCA carriers in the region informing them about the support groups, asking what they would want from the group and the best day, time and location. Our first two support groups were held during the evening in March 2013, at Guy's and Maidstone Hospital. Both groups were well attended and deemed, via patient feedback and validated evaluation, to have been very successful. There are also plans to hold evenings at Brighton and Canterbury Hospitals over the coming months. It is anticipated that the support groups will be held three times per year at each venue. A Macmillan Grant has enabled us to provide refreshments at the meetings and to reimburse the steering group members' travel expenses.

The Trust PPI team have provided guidance about the role of the Steering Group members and will also provide training, free of charge, in research matters and chairing meetings. The London South CLRN is actively supporting these activities as raising awareness and understanding of research has been a central aspect of this whole process and continues to be an important area for the Steering Group and the support groups.

After each Steering Group and support group meeting we have reflected on the session from an organisational and a counselling perspective. Also, Caroline Langman attends regular clinical supervision. Setting up and sustaining such a group is not without its challenges, many of which we are still working on and we will continue to review how things are going over the coming months. This is, however, an exciting development that appears to meet the needs of our patients and we are grateful to all who have been involved.

Preimplantation genetic diagnosis for cancer syndromes

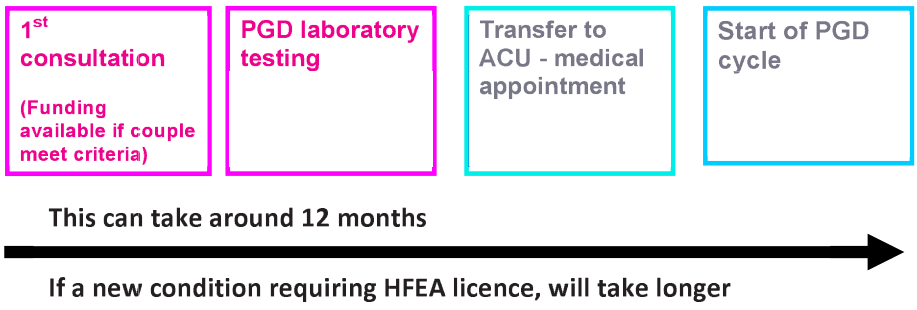
Alison Lashwood, Centre for PGD, Guy's Hospital, London

Preimplantation genetic diagnosis (PGD) has been available for over 20 years, yet it is only more recently that requests have included cancer and cancer predisposing syndromes. The first such case of PGD for BRCA1 was reported in 2008 and since then the number of cancer related conditions licensed by the Human Fertilisation and Embryology Authority (HFEA) has increased significantly (http://www.hfea.gov.uk/cps/hfea/gen/pgd-screening.htm). In the UK each centre offering PGD must have a licence from the HFEA and each genetic condition for which PGD is offered must also be licensed for practice. Currently we can offer PGD for FAP, HNPCC, MEN1 and MEN2a, RB1, NF1, NF2, BRCA1 and BRCA2.

PGD offers couples an alternative reproductive option. The uptake and view of prenatal diagnosis (PND) for cancer syndromes is low, given the often later onset nature of the disease, the lack of penetrance and the treatability of some forms of cancer. Certainly the issue of termination of pregnancy in such cases raises some additional dilemmas. Many couples consider the destruction of embryos as quite different morally, socially or religiously from termination of pregnancy and therefore PGD appears to offer a more acceptable option. The family experience of the disorder will have a major impact on how the couple view the illness and whether they decide to avoid transmitting the gene to future generations.

The PGD procedure

Prior to a treatment cycle there are several stages involved in preparing a couple for treatment.



Centres offering PGD will vary in both the type of analysis they offer as well as the process of a treatment cycle. The aim of treatment is to stimulate the ovaries to produce a number of eggs that can be fertilised with the partner's sperm. Three to five days after fertilisation 1 or 2 cells will be biopsied from the embryos and analysed for the familial disorder. Unaffected embryos with suitable morphology will be considered for embryo transfer and one or 2 embryos transferred into the uterus. A resulting pregnancy should be unaffected with the specific genetic condition and a healthy child born.

Embryo analysis

We use a linkage based approach (PG-Haplotyping) for all monogenic disorders and as such the development of the test for each couple will require blood/DNA samples from the couple and usually the parents of the affected partner. Generally the chance of misdiagnosis is less than 1%.

We are not able to offer PGD when the disorder is de novo or other family members blood/DNA are unavailable as we are then not able to set the phase of the markers for our linkage analysis. Other centres use different technology so can offer PGD for de novo cases. In time, if we move to an alternative form of analysis, this may be possible. We would recommend that if you are in any doubt as to the suitability of the family structure for PGD that you call us to discuss before referral.

Success rates

Success rates in PGD vary and several factors can have an impact on the outcome such as female age, gynaecological history and BMI which will affect ovarian reserve. It is important to assess potential ovarian reserve early on in the preparation for treatment so that couples are informed if PGD success is likely to be sub- optimal. It is important to be open with couples and if there are concerns about likely success rates from the start then the couple will be discouraged from going through a cycle.

"The family experience of the disorder will have a major impact on how the couple view the illness and whether they decide to avoid transmitting the gene to future generations"

Success rates: 1997- December 2012

Cycles started	1487
Cycles to embryo transfer	1055 (71%)
Clinical pregnancies	432 32% per egg collection 41% per embryo transfer

Babies born

Singletons	326
Twins	121 (61x2)*
Triplets	15
Total	462
46 on-going pregnancies	

*1 IUD

What else needs to be considered?
As most of the cancer syndromes are inherited in an autosomal dominant manner, the number of embryos required to ensure transfer is relatively high given that on average 50% will be affected. This means that ovarian reserve and likely egg production is reviewed carefully.

In accordance with the HFE Act (2008) any centre offering treatment must consider the welfare of any child born following treatment. Most of the couples we see who have a family history of a cancer syndrome are asymptomatic carriers, but some will have had treatment and may develop symptoms at a later stage. This in itself is not a reason to deny a couple PGD, but it is important to discuss the impact of parental health and wellbeing on the family and childcare plans for the future.

All couples undertaking PGD will be medically reviewed. Those who have been affected by a familial cancer may have already had treatment which will be reviewed by our team and the specialist looking after them will be asked to comment on the clinical safety of offering PGD. Due to the impact of past treatment, especially if chemotherapy has been used, couples may have had their gametes stored pre-treatment. It is possible to use stored gametes, but it will be important to assess this ahead of time.

Funding
A national funding policy for England PGD was introduced in April this year. The devolved nations have their own funding policies and require individual funding applications. However, in England, provided couples meet a set of criteria, they are automatically eligible for up to three cycles of PGD. This means that once they have achieved a successful outcome (i.e. a live birth) from PGD they will receive no further treatment. To meet the eligibility criteria means that the female's BMI is between 19 and 29; the couple are non-smokers; they have no healthy children of the current union; treatment must be completed by 40 years of age; there is a high genetic risk and an HFEA licence exists. For further extended details of the funding policy please see. http://www.england.nhs.uk/wp-content/uploads/2013/04/e01-p-a.pdf

The funding issue that remains unclear is where couples already have children who are at 50% risk of familial cancer(s). Technically we do not yet know whether the children are healthy or not. We have been advised for the time being that if PGD is requested in such circumstances we make an application on an individual case basis through an Individual Funding Request (IFR).

Referrals
We are happy to receive referrals and if possible would ask that you use our standard referral form, or use it as a guide to the information we require to assess a couple's suitability for PGD. http://www.pgd.org.uk/home.aspx

We also have a group email that you can use for general enquiries and as a team of five we hope that you will receive a timely response (PGDGenetics@gstt.nhs.uk). Please do not send referrals through this channel. If you prefer contact by telephone (and sometimes this is easier for in depth discussion) please call 020 7188 1364. We are always happy to help.

Dates for your diary

Andrew Cuthbert

The latest clinical guideline (update) from NICE on Familial Breast Cancer will be published on 25 June, with a press conference on the 24 June. An embargoed version of the guideline will be released on 12 June, available only to registered stakeholders who have returned a confidentiality form to NICE.

This year's British Genetic Medicine Conference is in Liverpool, at the Arena Convention Centre, 16 to 18 September. Registration is now open.

The 2013 InSight conference is being held in Cairns, Australia this year, 28 to 31 August. See http://www.insight-group.org/newsitem/28/ for more details.

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Editorial

The possibilities for genomics to impact population health are far-reaching and urgently require translation into public health policy to improve health outcomes. In this issue we bring you highlights from the Translating Genomics conference held in December last year as well as advances in cancer genomics from a population perspective.

I am delighted to introduce the articles for this issue of the SGPPH's contribution to the BSGM newsletter. Our first featured article submitted by Philippa Brice gives us a flavour of the sessions at the Translating Genomics conference, hosted by the Foundation for Genomics and Population Health (PHG), held to celebrate 15 years of public health genomics. This exciting conference addressed opportunities for genomics to improve population health and be adopted by health systems, and featured a host of world-renowned speakers.

Researchers at the Institute for Public Health Genomics (IPHG) at Maastricht University in The Netherlands will share with you the advances in public health genomics with a specific focus on cancer and personalised cancer therapy. In our second article, Henk van Kranen gives a clear account of current developments in personalised cancer therapy and future directions. Our final article by Bodo Lange and Angela Brand highlights the advances the Mutanom research project has made in identifying and characterising some of the most frequently occurring cancer mutations, while incorporating a Systems Biology Model which predicts the response of cancer cells undergoing treatment.

I do hope you enjoy reading this issue. I'd like to thank each of our authors for their exciting and well-written articles, without which this newsletter would not be possible. For further information regarding the work of the PHG please visit http://www.phgfoundation.org/ and for the IPHG at Maastricht University please email Professor Angela Brand at a.brand@maastrichtuniversity.nl. More Information on the work of the IPHG can be found under www.phgen.eu, www.itfom.eu and www.mutanom.org.

For all those interested in writing for us, please be in touch. I look forward to bringing you our next issue.

Dr Angelique Mavrodaris

Translating genomics: 2013 and beyond

Dr Philippa Brice,, Foundation for Genomics and Population Health, Cambridge, United Kingdom.

Last December the PHG Foundation hosted the Translating Genomics conference, the culmination of a series of events to mark our fifteenth anniversary in 2012. We were pleased to welcome many BSGM members to this event, which had a particular focus on the challenges of making genomic science work for individual and population health.

Speakers examined the specific opportunities for genomics to improve population health practice in the context of cancer treatment, cardiovascular disease management, and for obesity. We have now published a report, Genomics of obesity, in which we make recommendations for the use of genetic testing in current services for obesity. We show where genomics can form an important element in the investigation of patients with features indicative of potential monogenic obesity, whilst clarifying that the application of genomics for common, polygenic cases has no current clinical utility – although of course research in this area is very valuable for advancing our understanding of obesity and related mechanisms!

Professor Dennis Lo

Following an exciting keynote presentation from Professor Dennis Lo on his brainchild, non-invasive prenatal diagnosis (NIPD) 'from dream to reality', the conference considered the steps needed to move genomic innovations from bench to bedside. NIPD has of course progressed rapidly towards clinical practice, but bringing new technologies (however advantageous) into health services is rarely straightforward. Delegates heard expert perspectives on key areas that influence progress towards uptake – clinical considerations, industry aims and priorities, the increasingly crucial field of bioinformatics and the broad church of policy. This led into a discussion of likely future directions for health applications of genomics, and our preparedness (or otherwise) for such developments.

Dr Muin Khoury

Dr Muin Khoury of the PHG Foundation's renowned US counterpart, the National Office for Public Health Genomics within the Centers for Disease Control, gave a closing keynote address on the ongoing importance and urgency of translating genomics into public health benefits. Anyone who missed the conference but would like to hear some of the speakers can view edited highlights via our website at www.phgfoundation.org.

After the conference we enjoyed a splendid meal in the great hall of King's College where after-dinner speakers Professor Dame Sally Davies and Professor Sir Leszek Borysiewicz commended the value of genomics for population health and the NHS; genomics really is commanding the attention it deserves at the highest levels.

Where next for the PHG Foundation? Our anniversary publication, Beyond the horizon: Connecting science and health, not only looked back over how far genomics has moved, but also set out some of our future directions. As a policy think-tank, our main focus remains firmly with genetics, and our aim is still "to do all we can to see that everyone benefits from high quality genetics services in the UK and beyond". We look forward to continuing to work with BSGM members to achieve what we hope is a shared goal.

Dr Ron Zimmern, Chair, PHG Foundation; Professor Dame Sally Davies, The Chief Medical Officer, Dr Hilary Burton, Director, PHG Foundation and Professor Sir Leszek Borysiewicz, Vice Chancellor, University of Cambridge

The translation of Systems Biology Modelling and Next Generation Sequencing in a clinic setting for the development of new approaches in personalised cancer medicine - the Mutanom project

Bodo Lange,, Alacris Theranostics, Berlin, Germany and Max Planck Institut für Molekulare Genetik, Berlin, Germany
Angela Brand, Institute for Public Health Genomics, Maastricht University, The Netherlands

For most of the 1.7 million people dying annually of cancer in Europe (2006), mutations and structural genome variations play a key role for disease development and progression. While most of the mutations and variants that accumulate over the lifetime of a person are harmless (also called "passenger mutations"), a particular set of "driver mutations" can lead to cancer or metastasis.

The research project Mutanom (www.mutanom.org) has identified and characterised the functional consequences of some of the most frequently occurring mutations in breast, gastrointestinal and prostate cancer[1]. The mutations were identified in the Catalogue of Somatic Mutations in Cancer (COSMIC) database or through next generation sequencing (NGS) of tumour samples from patients. Consequently, the consortium generated a large series of isogenic cell lines into which selected wild type or mutant forms of the cancer genes were introduced to analyse the effects on cancer related traits and signalling.

The work revealed new protein interactions to oncogenes and tumour-suppressors and subsequent alterations in cancer specific signalling and cell proliferation events (for example in the PIK3/AKT and RAS/MAPK pathways) via functional genomics, yeast two-hybrid and quantitative mass spectrometry approaches[2,3,4].

A predictive Systems Biology Model is integrating quantitative molecular information obtained from our experiments, databases and from clinical data including genome, transcriptome, epigenome, micro-RNA and phosphoproteome data. The model provides testable predictions for drug treatment of cancer cells, identifies new drug targets and improves our understanding on the action and side effects of drugs on cellular signalling pathways[5,6,7].

As part of the project, academic experts in public health genomics (Public Health Genomics European Network, PHGEN) have been ensuring that the translational aspects of the project are efficiently progressing and exploited[8]. We expect the overall approach of Mutanom to become a key instrument in improving diagnosis and therapy of cancer and many other complex diseases.

During the course of the project the Systems Modelling approach was developed far enough and led to the founding of the company Alacris Thernaostics (www.alacris.de) that will apply this technology in research projects in clinic settings (www.oncotrack.eu) for the prediction of optimised individualised drug treatment of colon cancer patients.

This translation shows that next generation sequencing analysis of cancer genomes (transcriptome and whole genome) combined with predictive modelling provides is now at the stage of clinical application.

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Personalised cancer treatment: present status and future developments

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From extensive molecular genetic analysis of a variety of different cancers, it is becoming increasingly clear which driver and passenger mutations are involved in various types of cancers[1,2]. This also confirms the metaphor of Darwinian micro-evolution in cancer, providing each tumour with a unique set of genetic alterations (and gene expression profiles). Major driver mutations have guided the development of drugs specifically targeted at corresponding genes. This, among other factors, has recently resulted in a series of startling clinical studies that have brought molecularly targeted therapies to the management of diverse cancers. Among the many examples are various kinase inhibitors, inhibiting B-RAF, ALK, PI3K and others, resulting in increased efficacy in the treatment of respective melanomas, a subset of non small cell lung cancer and a subset of B cell malignancies[3,4].

In addition, gene expression analysis of tumor biopsies has resulted in the development of prognostic and predictive biomarkers during the last decade[5,6]. For example, MammaprintR was the first FDA-cleared (IVDMIA) breast cancer recurrence assay based on a unique 70-gene gene expression signature. Along these lines similar efforts for other major cancers are ongoing.

More recently it was discovered that certain targeted drugs are much more effective on the subset of tumours containing an activating mutation in the corresponding oncogene, a phenomena known as 'oncogene addiction'[7]. This initiated the present era of tumour genotype-directed cancer therapy, delivering the most effective drugs to the right patients thereby holding the promise of greatly improving cancer survival[6]. Eventually, this approach results frequently in acquired resistance to the targeting agent. This is not surprising considering the many (interconnected) pathways involved. The significance and interplay of all these different pathways have cumulated in a working model known as 'The Hallmarks of Cancer[8]'. The difference in tissue specificity of similar genotypes for the same drug (differences between melanoma B-RAF and colorectal cancer B-RAF mutated tumours) was also recently explained by differences in EGFR expression between these tissues[5].

Switching from single genotype direct therapy towards more pathway genotypes-directed approaches could be an approach to narrow down the escape possibilities of a tumour[5]. Finally, these developments have initiated the foundation of the Center for Personalized Cancer Treatment (CPCT) in 2010, a union of the three largest cancer centres in the Netherlands with the ambition to become one of the World's leading providers of personalised cancer treatment.

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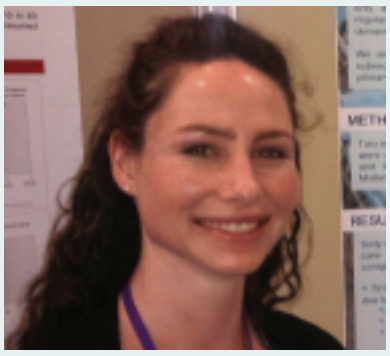

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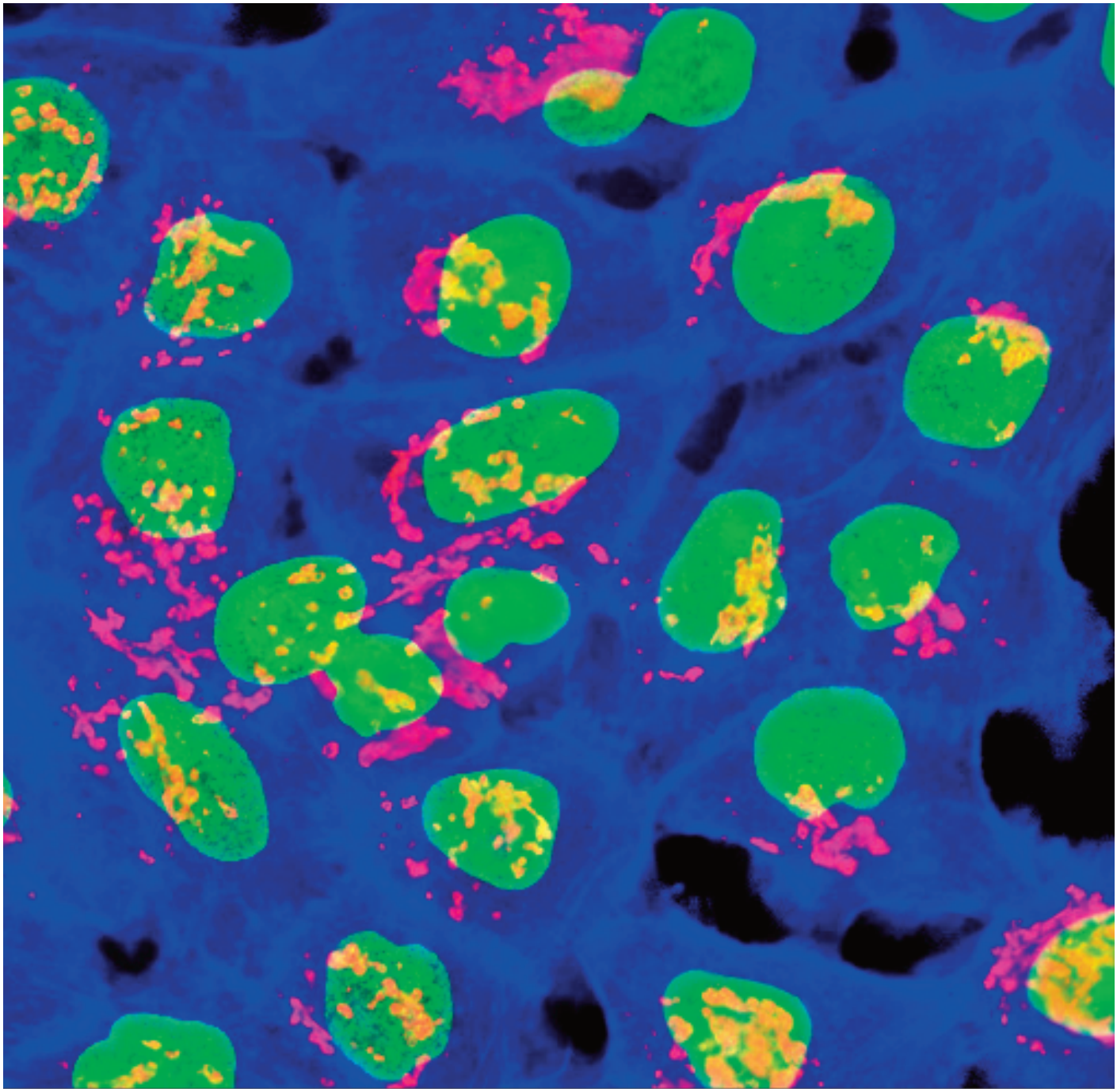

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