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ADELPHI GENETICS FORUM

exploring heredity and society

Adelphi Review

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Adelphi Genetics Forum, 19 Northfields Prospect, London, SW18 1PE

Tel: 020 8874 7257 www.adelphigenetics.org

General Secretary: Mrs Betty Nixon
executiveoffice@adelphigenetics.org

Review Editor: Mr Robert Johnston
Charity No: 209258

EDITORIAL

Most of this issue is dedicated to a report on our recent Annual Conference on 'Progress and challenges implementing genomics into practice and society'. The day's programme was based around 2024 being the 20th anniversary of the publication of the completed sequence of the Human Genome Project (HGP) in *Nature*.

The various speakers described some of the achievements, hurdles and failures of the intervening period from a variety of perspectives. The event was very well attended and plans are already underway for our Annual Conference in 2025. You can view all the talks and slides on our website at: https://adelphigenetics.org/events/annual-conference-2024/.

On page 22, there's a fascinating account of a science enrichment club at The Thomas Hardye School in Dorchester, dedicated to introducing secondary students to the exciting field of molecular genetics. The club is run by **Simon Lewis**, a member of the Adelphi Genetics Forum, who attended last summer's Teachers' Conference. This undertaking is a remarkable achievement and as a secondary teacher myself, I applaud his dedication and tenacity in running such an undertaking in difficult financial times.

Finally, we have an interim report from **Andrew Walton** from University College London, whose PhD the Forum is sponsoring. It's early days and we look forward to further feedback next year.

Robert Johnston

The Adelphi Genetics Forum Annual Conference

Progress and challenges implementing genomics into practice and society

16 October 2024 at the Royal Society

As always, this year's conference was held in the Wellcome Trust Lecture Hall of the Royal Society. The full programme is available on our website at https://adelphigenetics.org along with a link to videos of the talks and slides.

The President, **Professor Nicholas Wood** opened the conference and welcomed the various speakers and attendees. He also thanked the organisers for all their hard work, **Professors Shirley Hodgson and Anneke Lucassen and Dr Helen Middleton-Price**.

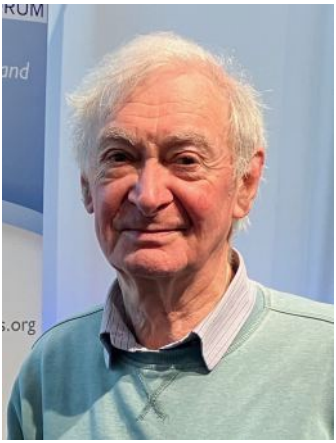
The first session was chaired by **Dr Helen Middleton-Price** who introduced **Professor Andrew Read (University of Manchester)** whose talk was titled **"The Human Genome Project - 20 years on"**. Professor Read divided his talk into three main areas: **Before** – human molecular genetics research in the 1980s and 1990s; **During** – what the Human Genome Project (HGP) did and didn't achieve, and **After** – developments since the completion of the HGP.

Before

He referred to his own research on Waardenburg syndrome (WS1), a condition characterised by a patchy absence of melanocytes. Firstly, he needed a dedicated clinical collaborator to find and diagnose the multicase families. The common approach was 'positional cloning': first, the families were subjected to linkage analysis, looking for DNA variants that track through families alongside the condition. This found the gene for WS1 to

lie on the bottom of chromosome 2. But there were many genes in this region, and identifying all these before the HGP was a major undertaking. The correct gene was found to be *PAX3*, which carried mutations in nearly all the cases of WS1, with the range of variants allowing inferences about the pathogenic mechanism.

So, before the HGP, research was targeted and hypothesis driven, with many individuals working on small-scale projects in different centres; there was a close working relationship between clinicians and scientists, and results would move seamlessly into clinical service.



Professor Andrew Read

During

Then came the HGP; there were objections that this was not real science, and that it would take money away from disease-based research. Some identified it as a centralised, mindless, industrial scale endeavour. The 'completed' HGP was published in 2004, following the initial sequencing and analysis of the human genome in *Nature* in 2001. It was a massive project involving thousands of researchers in different countries: while each cell has six billion base pairs (bp) of DNA, the largest piece that can be sequenced at one time was up to ~700bp. There was lots of hype – for example, over 25 years ago the eminent scientist-clinician Francis Collins, and others, predicted that in 10 years 'medicine will move from a diagnose and treat model to a predict and prevent model'. This has yet to be realised. Also, the science of 'genomics' was born – the study of the functions and interactions of all the genes in the genome, contrasting with 'genetics' – the study of single genes and their effects.

After

The key features of the post-HGP landscape are: Big Science – with research consortia working collaboratively, focussing on the whole genome and working towards creating a data rich environ-

ment. There were crucial technical developments, such as Next Generation Sequencing (NGS), increasing the speed of genome sequencing. Then, genome editing technologies were developed alongside single cell technologies, so that the DNA of single cells could be manipulated. The implications have been:

Cell biology

One of the critical questions of cell biology was answered by the HGP: in the 1990s, we expected the human genome to have around 100,000 genes. However, the 2004 paper found only 22,287 protein coding genes, a similar number to the worm *C. elegans*. We now know there are more *non-coding* genes than protein coding genes; although this number is similar in humans and worms, we have many more long non-coding (lnc) RNAs (>200nt long, known to be involved in gene regulation), and we have four times as many gene transcripts, so we use protein coding genes in more complex ways. Therefore, our complexity is to do with complex and subtle gene regulation mechanisms that we are now beginning to understand.

Population studies

The HGP data were generated from a small number of white males. To get a picture of the variation of genomes, we must examine many different genomes, in projects like the Human Variome Project. Further to this, there have been large statistical studies to study population structure, revealing information about evolution, ancestry, population origins and movements.

Medicine and therapy

In cancer, there has been spectacular progress in the last 20 years. We know that mutations in many genes can cause cancer, but the effects are largely in about a dozen different pathways. We now have a good understanding of the cell biology of cancer, leading to the development of personalised treatments. In contrast there has been limited progress in other conditions, for example, autism and schizophrenia.

In drug development, the hope was that the HGP would revolu-

tionise drug development by identifying new targets, which has largely not happened. However, new technologies have enabled huge genome wide association studies (GWAS), identifying DNA variants that are associated with certain common diseases.

Professor Read concluded that we now have a new view of our human genome, and a deeper understanding of our cell biology, leading to active interventions. The challenge is to move to a systems level understanding of the whole human being.

Following a break for coffee, **Professor Anneke Lucassen** chaired the second morning session and the first speaker was **Dr Sarah Wynn (CEO at Unique)** who spoke about **"The promises and challenges of genomics for patients and families affected by rare conditions"**. She started by describing the length of time it takes to obtain a diagnosis for patients and families with rare conditions, then went on to recall **what has changed in the last 20 years**. These include: 1) the decline in the cost of sequencing due to the use of next-generation sequencing technique which she depicted with the Moore's Law chart; 2) research on rare diseases in the UK with a focus on neurodevelopmental disorders, supported by Unique; 3) the Deciphering Developmental Disorders project; 4) the 100,000 genomes project; 5) the Generation project; and 5) Policy and Service delivery which has resulted in the NHS Genomic Medicine Service.

Dr Wynn illustrated other changes that have occurred in the last 20 years with figures from her organisation, Unique. In 2004, Unique had 4000 members with rare chromosome disorders and the organisation had produced 7 information guides. Now Unique has over 30,000 members, over 600 members with a diagnosis of a single gene disorder, and more than 540 information guides in 22 different languages.

She explained why getting a diagnosis is important for families: 1) This reduces the diagnosis odyssey where patients and families undergo difficult years of various tests in order to obtain an

accurate diagnosis; 2) the name of the child's condition is known; 3) this helps with reproductive decision-making; 4) patients and families can get support and share data; 5) there is the chance to network with other families in the same situation; and 6) having peace of mind and relief of guilt. To illustrate this, she showed extracts from sentiments that are expressed when families obtain a diagnosis.


Dr Sarah Wynn

Dr Wynn went on to explain that a lot of effort has been concentrated on looking for coding genes as causes of rare conditions, but it is now obvious that non-coding genes contribute to neurodevelopmental disorders. She gave the example of *RNU4-2*/ReNU Syndrome which is caused by changes in the non-coding gene *RNU4-2*. It has been found that changes in this non-coding gene, *RNU4-2*, are quite frequent, being observed in 0.5% of undiagnosed patients with NDD (i.e., in 70 families). There are podcasts, Facebook groups, and other social media discussions about this new discovery.

We also heard about hopes that families have for the next 20 years. This included 1) quicker diagnosis; 2) equitable and wider access to genetic testing; 3) treatments and therapies that are targeted and safe; 4) possible cures; 5) services and support; and 6) some understanding from all who are involved.

Dr Wynn ended her talk with a summary of what is still needed and ongoing developments. She mentioned: 1) 50% of patients with neurodevelopmental disorders are still undiagnosed; 2) improved management and coordination of care was required; 3) the involvement of AI in medicine and genomics; 4) projects that Unique was engaged in with the University of Manchester and

Shorthills in India; and 5) applying technology to assist in the production of information for patients and families as they are only a team of two people tasked with producing all the information they put together for patients and families.

The next speaker was **Professor Clare Turnbull (Institute of Cancer Research)** who described **"Genomics in population screening for cancer: opportunities, challenges and cautions"**. Genomic studies have been extensively used in the study of cancers at individual and population levels. It is widely accepted that the ability to diagnose cancers at the earliest stages is most likely to improve treatment options and outcomes. Screening for the incidence of cancers, especially the more common cancers, is therefore highly desirable.

The National Health Service has set the ambitious target of detecting 75% (currently at 54%) of all cancers at stage 1-2 by 2028. Improvements are needed in screening procedures that are often complex, expensive and not always effective clinically. Careful selection of the cohorts who would most benefit from screening is essential.

Her talk focussed on exploring the factors to be considered for the effective implementation of population screening but contrasted this with the successes of family-focussed screening, for example where BRCA1/BRCA2 mutations had been identified. Generally, cancers arise at older ages. The current population screening strategies include offering breast cancer screening by mammography for 50–70-year-old women, and colorectal cancer screening by faecal immunochemical testing, biannually between ages 60 to 75. However, to detect early stage, often more aggressive cancers at younger ages would save more life years. But the population to be screened would balloon to impossibly large numbers. Therefore, it would be useful to be able to stratify the broader age span group through some knowledge of likely predisposition.

Recent large population studies have identified genome-wide associations of combinations of single nucleotide polymorphisms (SNPs) with disease incidence. This work feeds into the derivation of personal polygenic risk scores (PRS) for different cancers. The work is ongoing and so the PRS details for each cancer are fluid. However, currently 331 SNPs are associated with breast cancer and 87 with colorectal cancer. Can PRS values be used to stratify the population effectively and extend the screening to younger-age predisposed individuals? Modelling the outcomes for breast cancer showed that

Professor Clare Turnbull

by testing the top 20% PRS risk cohort from age 40, 37% of the true incidence would be detected in this way, but with 20% false positives identified and 63% of cases would be missed, mostly among the unscreened low-PRS-risk individuals. The total number of extra lives saved using this strategy would be rather small and there would be complex issues of false positivity and missed cases to be dealt with. Part of the reason for the relatively poor performance is that the heritability of breast and other common cancers is fairly low so that most of the incidence is actually in low -risk individuals. The additional identified cancer incidence using the top 20% of PRS risk is relatively small and the number of averted deaths even smaller.

Similar analyses were discussed for colorectal cancer and prostate cancer. For the latter, one highly relevant factor in the relatively poor performance of the screening strategy is that the screening test, measuring Prostate-Specific Antigen (PSA) levels, is not very effective. There is significant over-diagnosis requiring extra test follow-up and sometimes resulting in debilitating unnecessary treatment. In a significant proportion of identified cases the disease is actually indolent so the patient would die of other caus-

es before the tumour killed him/her. There is, therefore, a significant need to develop better screening tools in most cases. This is certainly very relevant for some of the more acutely lethal but rarer cancers such as pancreatic. The incidence of different cancers in the screened population also strongly affects the efficacy of the programme.

To raise the effectiveness of PRS, other criteria could be bolted on to select cases for intensive screening (for example more frequent imaging or additional tools such as MRI screening in addition to radiological). Family history could be included, but additional multimodal criteria would make the delivery of consistent screening much more complex. People's behaviour in coming forward for screening and how they react to the results conveyed are also variable. Modelling the predicted outcomes for screening shows that the gains in terms of life years saved are in most cases disappointingly small and dealing with overdiagnosis is also a problem, as is the substantial incidence among the low-risk un-screened cohorts.

The final speaker of the morning session was **Professor Michael Parker (University of Oxford)** whose talk was titled **"The changing moral life of genetics and genomics since the Human Genome Project"**. He began by considering his own story and how he became involved with ethical issues in genetics research, a fascinating field to study.

He gave examples he encountered to illustrate the complexity of the issues that can arise. Firstly, a case where one of two twins was tested for Huntington's but should the other twin be told of this? Secondly, where a newborn baby was found to have a severe autosomal recessive condition but on testing the parents for future children, discovered that the father could not be the biological father. Both of these led to ethical dilemmas. Such cases must always be patient-centred, but should families also be included? Another challenging area is the complex issue of applying genomics in areas of Africa where malaria is endemic with the inevitable links to sickle-cell disease. Some of these

cases have again revealed disputed paternity – who is entitled to know?

Professor Michael Parker

Professor Parker has been the ethics lead for a number of organisations related to genetics including the 100,000 Genome Project and Our Future Health. Then in 2018 he joined, as ethics advisor, the Nuffield Council on Global Health Emergencies. This inevitably led to a position on SAGE throughout COVID where the challenges of considering the evolution of new variants seemed never ending. The next phase is preparing for the next pandemic by studying the phylogenetics of viruses. This is a collective effort which requires better surveillance and is part of the responsibility of the Pandemic Sciences Institute at Oxford.

He closed by posing some questions:

·Can we find ways to build consideration of ethical issues and value judgements into the day-to-day work of practice and policy?

·How can we support scientists with the discussion of ethical issues in their work?

·How do we address value differences between countries?

Following lunch, the first session was chaired by **Professor Dian Donnai** who introduced the first speaker, **Professor Bill Newman (University of Manchester)**. He discussed **"Implementing pharmacogenetics at scale in clinical practice"**. He started by mentioning his support of clinical genetics, and the diverse team of experts in different fields with which his work interacts.

We were then taken through the reasons some people fail to respond to drugs or suffer side effects. This included 1) people living longer and taking many drugs that interact with each other; 2) peo-

ple not adhering to taking drugs as they should; 3) inherent differences between people which means the same drug will not work for the same condition; and 4) people taking other supplements that then interact with prescribed drugs and cause side effects.

This area of study started when it was noticed that American soldiers from the Korean war, who received treatment for malaria, developed haemolytic anaemia due to the lack of the enzyme G6PD (glucose-6-phosphate dehydrogenase). He mentioned that the Cytochrome P450 enzymes (known as CYPs) are involved in the effects of drug treatment.

Professor Newman went on to set out the scene in the UK, that in 2004, there was a government document on "Our inheritance, our future" which resulted in a focus on pharmacology, with five projects funded. Out of over 500, there are only 4 gene-drug therapies in the UK. He showed the common drugs taken in UK as being ibuprofen and statins. In order to make progress with identifying people who will respond well to treatment and those who will not, a study that came out in 2023 that advocated testing people on a group of genes, rather than testing one gene at a time.

We learnt about three different models regarding treatments: 1) the Reactive model which is used at present and involves point-of-care tests; 2) the Reactive with planned Reuse model; and 3) the Pre-emptive model, where everyone has their information on drugs that work for them, and they carry this information around so it can be referred to when required.

Professor Newman gave the example of a child with cystic fibrosis who gets genetic testing and will require antibiotics later in life. With information from the genetic test, it is known that this child will develop hearing loss from certain antibiotic treatment, so an alternative drug can be given to avoid hearing loss. He spoke about the rapid test that has been developed for the *RNR1* gene that is involved in hearing loss, because results and

treatment must start within one hour of when a child is admitted into the newborn unit. We learnt that this test is based on LAMP (**L**oop-mediated isothermal **Amp**lification) and is not PCR-based, and that these cases do not require informed consent because of the urgency of the situation. The test for the *RNR1* gene from a cheek swab takes only 26 mins and this is the current practice. He indicated that other areas that they are looking to apply this test is in the treatment of strokes.

In future, the plan is to use the 'planned reuse'/'pre-emptive' models and funding has been obtained for a study called **P**harmacogenetics **R**oll **O**ut – **G**auging **Res**ponse to **S**ervice (PROGRESS). The purpose is to find genetic changes that interfere with the effectiveness of drugs that are commonly prescribed, develop the right laboratory test, and explore how to move information on test results from the laboratory to the clinic. The study is also meant to explore the possibility of implementing this as an NHS-wide service that would save lives and the huge amounts of money currently wasted on dispensing drugs that do not work for everyone.

Professor Newman spoke about the importance of data that will enable future plans to work, and that moving data is complicated. He addressed the question of what people, health experts, and the public need, and indicated the requirement for information to be understandable. He elaborated on how the system of integrating laboratory and clinical data would work. This requires moving information from the laboratory into a clinical data storage system that contains phenotype data (clinical information about the patient), and is understandable, i.e., the **E**lectronic **H**ealth **R**ecord (EHR). Each time test results are entered for a patient, an alert is received for that patient in the

Professor Bill Newman

form of a traffic light system, where RED indicates that there is an issue to be noted, and GREEN indicates all is OK. He confirmed that the system is now up and running in the North East.

The next aspect Professor Newman addressed was on **how to deliver the service**. He presented outcomes from a study of 2,500 members of the public and 300 health professionals which indicated that: 1) the public would be happy to participate and provide cheek swabs; 2) they would want to access their data on an app; and 3) they would be happy for the information to be used by their GP. The responses from doctors and pharmacists indicated that they would like the test results to be entered straight into the EHR system and the implications clearly stated so that they do not have to investigate what results mean, as is the situation with current genetic testing reports.

We learnt that the outcome from the PROGRESS study so far indicates that 28% of people will require different drugs. Evaluations have started with statins, and future/pre-emptive testing will start with older people who tend to be taking more drugs.

Professor Newman ended his talk with the following points: 1) the use of pharmacogenomic testing is increasing; 2) testing is moving away from single gene/single drugs; 3) pre-emptive testing is being introduced; 4) there is the opportunity for saving lives and improving clinical outcomes; and 5) this type of work encourages interactions between geneticists and pharmacists.

Next, **Professor Anne Ferguson-Smith (University of Cambridge)** discussed **"Epigenetic inheritance – models and mechanisms"**. Her presentation focused on epigenetic inheritance, exploring its models, mechanisms, and significance in phenotypic variation and variable expressivity. She highlighted the interplay between genetic and epigenetic factors in controlling genome function, with particular emphasis on DNA methylation, histone modifications, and their roles in genome stability, gene expression, and phenotypic outcomes.

She reminded us of the key concepts in epigenetics, including its ever-changing definition, referring to chemical modifications on DNA: DNA methylation (addition of methyl groups to cytosine bases, primarily at CpG dinucleotides) and histone modifications (chemical changes to histone proteins) that affect chromatin compaction and accessibility so that histone proteins can influence genome function without altering the DNA sequence itself. She defined the major roles of epigenetic modifications as: (1) organising chromosomal architecture into heterochromatin (tight, repressive regions) and euchromatin (open, active regions); (2) dynamic regulation of gene expression to maintain heritable patterns in specific cell lineages, (3) control over repetitive sequences like transposable elements to preserve genome integrity. Further, she went on to explain the molecular mechanisms behind DNA methylation deposition, timely erasure, reconstruction and maintenance.

Professor Anne Ferguson-Smith

Exceptions, such as imprinted genes, escape erasure to retain epigenetic memory, leading to the paradigm of epigenetic inheritance, where certain genes are expressed depending on their parent of origin. In these cases, the imprint is established through differential DNA methylation during gametogenesis (male vs. female germlines) and maintained post-fertilisation. It is also controlled by specialized proteins (e.g., KRAB zinc finger proteins) that protect imprints from methylation erasure during early embryonic development.

The Epigenetic Regulation of Transposable Elements (Repetitive DNA) was also discussed. She highlighted the fact that certain transposable elements exhibit variably methylated regions (VMRs), contributing to phenotypic variation. She paral-

lelled these epigenetics findings, predominantly performed in mice, to the significant variability existing between human populations, with implications for understanding phenotypic diversity and susceptibility to disease.

She reminded us of the clinical and evolutionary implications of epigenetic mechanisms, including major contribution to phenotypic variation via variable gene expressivity, where individuals with identical genetic backgrounds display diverse traits or disease outcomes. This variability is influenced by both environmental factors and inherited epigenetic states. In humans, the variability in KRAB zinc finger proteins and repetitive element regulation may underlie differences in gene expression, health outcomes, and disease predisposition among populations. Insights from epigenetics could therefore advance personalised medicine by addressing the interplay between genetics, environment, and epigenome regulation. Professor Ferguson-Smith concluded by emphasising the vast potential of epigenetics in understanding human biology, evolution, and clinical outcomes, bridging basic research and medical applications.

The next session was chaired by **Professor Shirley Hodgson** and the speaker was **Professor Fergus Shanahan (University College Cork)** whose talk was titled **"No stool left unturned – why our microbiomes differ"**. Professor Shanahan provided a very different approach to the study of human variability: that which is related to the importance of the gut microbiome.

He began his talk by presenting the early evidence for the importance of the gut microbiome in disease susceptibility, with the finding that *Helicobacter pylori* infection was a risk factor for gastric ulcer and cancer. He also observed that experimental animals reared in a germ-free environment had completely different disease susceptibilities from their litter mates with microbially colonised guts. He stressed the role that the gut microbiome plays in food digestion, metabolic pathways and education of the immune system. He maintained that without knowledge

of the gut microbiome in an individual, one has an incomplete view of the whole individual.

However, it is not possible to say what a “normal” microbiome is, especially as the demands on the microbiome differ in different environments. He explained that the microbiome changes quickly, and is tractable, giving the example that people exposed to dietary restriction develop a microbiome which maximises the efficiency of calorie extraction from food, but such individuals tend to become obese and prone to diabetes if they migrate to an environment with no food restrictions.

Unfortunately, there is a dearth of information about the microbiome in non-affluent countries compared to studies in Europe and the US, making it difficult to derive a complete picture as to how the microbiome relates to diet, lifestyle and health in different environments. However, there are clear success stories, such as the treatment of *C. difficile* gut infection with faecal transplantation, and the success of eradication of *H. pylori* in reducing peptic ulcer diseases and gastric cancer. A normal microbiome is not necessarily a healthy one.

Professor Shanahan explained that the microbiome of an adult is largely established by 3 years of age. This could be compromised by repeated antibiotic use before that age. The microbiomes of adults become less diverse with age, with fewer protective taxa, which may be related to reduced contact with other people, animals and with nature, in addition to older people having a more restricted diet. This is related to increased ageing, gut inflammation and colon cancer risk. The specific microbiomes seen in

Professor Fergus Shanahan

these lifetime phases are being delineated, although there is still much that is unknown about this.

He discussed closed communities: It has been documented that the Amish have a much lower risk of atopic disorders and asthma, possibly linked to their microbiome, than the similar farming community, the Hutterites. The main difference between these groups is that the Hutterites live in an industrialised environment whereas the Amish have a very rural lifestyle, living in close contact with their farm animals. The non-industrialised microbiome has been found to be similar to the "ancestral microbiome", as determined from frozen or perma-frost preserved ancient faeces.

This begs the question as to the aetiology of differences in the microbiome. He described a study he had done on the microbiome of the Irish travellers, who make up 1% of the Irish population, and are neither Gipsy nor Roma. They used to live a nomadic lifestyle with large families, in crowded conditions in close contact with domestic and farm animals. They were found to have a microbiome very distinct from their more industrialised neighbours, resembling that of remote ethnic groups such as Peruvian, Nepali or Tanzanian populations. However, their microbiome tended to change towards that of their industrialised neighbours when they were moved into standard housing, although it was less affected if they were moved into "halting sites" where they could maintain a lifestyle more like the travelling type. Since the diet of these individuals was not "healthier" than that of their industrialised neighbours, it was concluded that the living environment of the travellers was more important than diet in the aetiology of their gut microbiome.

Following afternoon tea, the President, **Professor Nicholas Wood** chaired the final talk, the 3rd Adelphi Lecture (106th Galton Lecture), given by **Professor Steven Sturdy (University of Edinburgh)** on **"The fortunes of medical genomics: a quarter-century of promise"**.

His lecture provided a superb end-of-the-day complement to many of the earlier talks. In the first half, he reinforced Professor Read's judgments about the mixed successes of genomic medicine since 2000, with illuminating attention paid to the shifting of the promise of GWAS away from the discovery of cures for genetically complex common disorders (which proved a bust) towards its utility in advancing basic research and calculating polygenic risk scores. Once it was clear that nothing medically revelatory would emerge from GWAS there was, according to Professor Sturdy, a turn towards the genetics of rare diseases and cancer -- a move that brought a return to the sorts of collaborations with clinicians that, as Professor Read emphasized, were a feature of medical genetics in the pre-genomic days.

Yet even with this narrowing of the scope of the promise of genomic medicine, and despite stupendous levels of financial and human investment, the benefits to human health have so far remained modest. Why, then, has so much gone into creating such a vast medical genomics infrastructure? He said "The cost, is the point": a claim he elaborated in the lecture's second half, where he put the developments inventoried in the first half in a wider economic, political and moral framework by asking about the 'work' being done by all the over-promising.

He suggested, from the perspective of the UK government, the main attraction of a massively hyped and phenomenally well-resourced set of national institutions devoted to the cause of transforming genomic data provided by its citizens into medical breakthroughs, is the potential to attract the big pharmaceutical companies whose presence will make the UK a global leader in the life science industries. Within this model, the NHS becomes principally a site of innovation, patients become assets, and "informed consent" becomes ambiguous, because asked for in an atmosphere where patients are made to feel that there is a moral obligation to do all they can to help the around-the-corner breakthroughs that will save lives, if only enough people offer up their data.

In the lecture's final minutes Professor Sturdy placed genomic medicine as an economic project within a longer and wider context by pointing out that the predecessor science of eugenics was likewise an economic project, which valued human lives not as resources for a biomedical innovation economy but as productive workers in an industrial economy. The economic ends have changed, but the morally troubling over-promising has remained constant.

At the conclusion, the President presented Professor Sturdy with the Adelphi Plate.

Professor Steven Sturdy (L) and Professor Nicholas Wood (R) with Adelphi Plate

Classroom

Genetics as a vehicle for science enrichment

Testing burgers for horse meat, breakfast bars for nut contamination, and local ticks for Lyme Disease are just a few of the projects carried out in the Year 12 GENEsis Genetics club at the **Thomas Hardye School**, a comprehensive school in Dorset. The club allows students to develop technical skills, gives them opportunities to pursue individual interests via their own experiments, and exposes them to the wider scientific community.

Students taking part in the GENEsis club 2024-2025

The club has been running for ten years and is typically around 25 students who work in research teams. Each team consists of a small group of students, often friends, who collaborate and develop their skills over forty after-school sessions. The teams are provided with a box containing all the necessary equipment, a lab book, and a protocol folder. Each technique is demonstrated once by a teacher, students then carry out an experiment using the method. Written experimental protocols are then provided, with teachers available if needed.

Students start by learning basic molecular biology handling techniques. They are encouraged to demonstrate their aptitude with micro-pipetting by creating coloured liquid mosaics. Initial electrophoresis experiments involve casting and running gels to determine dye composition of “Skittles” sweets. Students then move on to purifying their own DNA using “mini-prep” kits This familiarizes them with centrifuges and other commonly used laboratory equipment. Purified DNA is used to carry out PCR, initially using primers for the Per3 allele, before moving onto a restriction digest to look at the Cyp450 allele responsible for metabolizing caffeine. DNA samples are stored in a -20^{o}C fridge between sessions.

After one term, students are sufficiently skilled to work on scientific questions of their choice. Recent projects have investigated the bacteria content of different milks and insect DNA contamination in flour. Students identify samples to test, extract the DNA and attempt to answer their questions. Successful and unsuccessful results are written up as posters and presented at a school science symposium and at the Institute for Research in Schools’ conference at Exeter University.

In the final term, Bournemouth University Scientists have supported students in carrying out DNA sequencing. Students isolated DNA from freshwater shrimp they collected on a fieldtrip. PCR is

used to amplify the COI allele with successfully amplified product being sequenced externally. Visiting Bournemouth University, students interpret their sequences, using freeware programs and the internet to produce a cladogram of evolutionary relationships.

There are three main obstacles for teachers wishing to run this type of club: financial, safety concerns, and the supply of appropriate primers.

All our costs are met through grant applications to support STEM in schools. Over the years, organizations such as the Biochemical Society, Rolls Royce, and The Royal Society have supported us. The most significant costs are the ongoing consumable costs of reagents and disposable plastics, totalling around £500-£1000 a year. Other capital equipment costs have been managed by buying secondhand equipment, such as a PCR machine, for £150. Donations from large local laboratories of unwanted pipettes have also helped.

The Health and Safety considerations of molecular biology research are less than they were twenty years ago. DNA stains such as “SYBR-Blue” are not mutagenic and using blue light rather than Ultra-Violet to visualize bands means these experiments can be run in a school with appropriate precautions. When investigating human alleles, samples are anonymized and no familial related DNA is used. This reduces the risk of genetic information being linked to individuals. The CLEAPPS guide *G272 Gene technology: A starter guide to health and safety* identifies many of the issues schools should consider.

Scientists who work with DNA regularly will design their own primers to amplify specific genes of interest, this is not feasible for students. Students can, however, identify published research pa-

pers from literature which contain similar studies to those they wish to complete. These proven primers can then be ordered online and we have had good success with replicating aspects of these previous studies.

Most of the students who take part in the club go on to study STEM linked degrees at university and for a few it has changed their goals to include biochemistry and genetic linked degrees. Their ownership of experimental work leads to obvious improvements in student laboratory autonomy when making decisions. The practical literacy skills needed to succeed as a scientist are also reinforced, lab books are completed weekly, literature searches are used to identify suitable projects and students need to write up and present their projects using scientific grammar and language.

As a teacher it can be challenging to network with other educational and science professionals. The club has visited the Public Health Laboratory molecular biology labs to see how they worked in West Africa fighting Ebola, collected environmental samples with Bournemouth University and presented at a Lyme Disease conference. Scientists from these organizations have subsequently visited the school. This network also extends to educational professionals met through travel to conferences such as “Science on Stage” or “ASE” to talk about the GENEsis club. Links made through the club will this year result in all A-level Biology students at the school completing the “Amgen Biotech Experience” using club equipment and consumables from Amgen to manipulate, ligate and visualize DNA

The GENEsis genetic club started small with a few micropipettes and some electrophoresis tanks, but over time it has become a school-based center for scientific research and excellence. It of-

fers students a technical challenge commensurate with their abilities and a window into a technology that will revolutionize society. We have found the GENEsis club to be beneficial in many ways, if you are thinking of starting a similar club, I would encourage you to do so, it is easier than you think!

Useful links

Slewis@thomas-hardye.net - This is my email, if you would like any help or advice about running a club like this, or feel you have some old equipment looking for a new home do please get in touch!

https://royalsociety.org/grants/partnership-grants/ - A good place to start looking for funding.

https://www.herts.ac.uk/study/schools-of-study/education/centre-for-stem-education/amgen-biotech-experience - Can loan equipment, consumables, and protocols for running genetic experiments in UK schools.

https://www.minipcr.com/blog/ - A fantastic resource to research any questions you might have about running and troubleshooting genetic experiments.

https://bento.bio/resources/labhome-vlog-series/ - An informative video introduction to the type of experiments you can run in a school.

Thanks to Dr Jeremy Rowe for running the club with me and to the many individual scientists and learned societies who have given their time and money supporting the club.

Simon Lewis
Thomas Hardye School, Dorchester

Adelphi Genetics Forum PhD Studentship: Year One Summary

I have really enjoyed the first year of my Adelphi Genetics Forum PhD Studentship. The first part of the year was spent researching the history and continued use of the panmictic population concept in Evolutionary Genetics. Drawing from published research, books and correspondence dating from the early 19th century, I have identified its first usage and early justifications. This revealed why the assumption of panmixia came to be established in the field and some of the implications of its continued usage. This work is in penultimate draft and will form the first chapter of my thesis.

In the later part of the year, I began work on a project to investigate how assortative mating affects allele frequencies. We are simulating different models of assortative mating under a range of assumptions about population dynamics, from panmictic to agent-based continuous space. I am currently writing up the initial results of this work with a view to submitting them for publication before the end of the year.

I have also been doing some empirical work, getting experience in using the tools I had written about earlier in the year which rely on the panmictic population concept. Specifically, determining the origins of a Roman-era British individual known as 'Beachy Head Woman'. The associated paper was submitted for review in early October.

Alongside this I have also been assisting with teaching on two courses at UCL (Science Communication and Genetics & Society), as well as delivering a talk about the teaching of Genetics in schools to the Adelphi Genetics Forum Teachers' Conference in Manchester earlier in the year.

Andrew Walton
University College London