Minutes of the First Ordinary Meeting

Held on Thursday 11th January 2018

Joint Meeting with the Liverpool Society of Anaesthetists

'Genomics and Tailoring Treatment for Patients'

Professor Sir Munir Pirmohammed, Professor of Molecular and Clinical Pharmacology, University of Liverpool

Professor Colm O'Mahony, Prof Sir Munir Pirmohammed and Dr Clare Howard.

LMI President, Colm O'Mahony, welcomed members of the LMI and LSA and introduced Prof. Pirmohammed and talked a little on their shared background when they worked together as junior doctors followed by LSA President, Clare Howard who then formally introduced the speaker.

Prof. Pirmohammed started his talk by saying that the drug budget for the NHS is increasing every year and currently stands at £18billion, the second biggest expenditure for the NHS. He said it costs $1billion to bring a drug into clinical practice but only 1:5000 compounds synthesised actually make it to market. More than 90% of drugs prescribed only work in 30-50% of patients. Patients are then made to wait varying intervals before trying alternative drugs so adding to morbidity and mortality. He said that adverse drug reactions are the cause of 6.5% of hospital admissions, happen to 15% of inpatients and cost £1billion per annum.

He described the different population needs, such as those patients with rare diseases, numbering about 3.5 million people in the UK. He also said that there is significant multi-morbidity accounting for 70% of all inpatient stays, with the average number of prescriptions per patient totaling 20. This represents a 15% increase in the number of items prescribed between 2005 and 2015. He thought drugs should better fit the patient with regards to the dose and its timing.

Prof. Pirmohammed said that there have been great strides made in genomics with the biggest advance being the sequencing of the human genome. This sequencing is identical in 99.9% of humans with only 0.1% being different, accounting for 3 million variations e.g. height and hair colour. He said that although there are 3 billion bases in the genome, the cost of sequencing it has decreased. Initially it had taken 13 years and cost $13billion to sequence the first but now it takes about 1 week and cost £600. He said eventually it will be available in a few hours, cost <£100 and be accessible to everyone.

He went onto talk about the concept of personalised medicine. We currently use phenotypic definitions e.g. ulcerative colitis, but we know that there are many types of ulcerative colitis allowing a molecular definition, which gives a better disease stratification. There is, however, still drug variability which is where pharmacogenomics comes in. Every patient is also different (impacted by environmental factors), so catering for all this is personalising medicine. He gave the example of cancer and said through sequencing technologies, driver mutations can be identified, making cancer essentially a genetic disease. He then gave the example of malignant melanoma and the BRAF inhibitor. Work undertaken in Cambridge showed that there was a driver mutation in the BRAF gene. A drug was developed to inhibit this mutation and eradicate the cancer. The trial size was small and the approval of the drug by the FDA was the fastest in history. So, by targeting and personalising therapy, we may be able to do smaller, faster trials.

Prof. Pirmohammed went onto talk about Cystic Fibrosis (CF) and the drug Ivacaftor, which targets the G551D mutation in the CTFR gene, which 4% of the CF population have. This drug gave patients an increase in FEV1, decreased hospital admissions and decreased respiratory infections. It however cost £150,000-200,000 per year. He said on the evidence of in-vitro data, the indication for the drug increased and the licence extended.

Prof. Pirmohammed talked about the 100k Human Genome transformational project and said that diagnoses have been made through genome sequencing. He spoke about how this sequencing translated to personalised medicine through some examples, the first being Childhood Motor Neurone Disease. In this disease, mutations had been identified in the SLC 52A2 and SLC 52A3 genes which are transporters of riboflavin. By giving patients high dose vitamin B2, a reduction in the deterioration of neurological abilities and improved survival had been seen in these patients. He said many advances have happened in the last year in the treatment of Haemophilia A, Sickle Cell Disease and Huntington's disease. He talked about genome editing and the ethical issues for human embryo editing with the fear of designer babies. He went onto talk about serious adverse drug reactions (ADRs) and how genotyping for certain drugs e.g. Abacavir, can be cost effective in preventing potentially fatal hypersensitivity reactions. He said that since 2004, there had been 24 serious ADRs associated with HLA alleles, but testing for these was not available in all immunology laboratories.

He described a gene panel that he had set up to develop HLA tests that cost <£20 with a turnaround time of <48 hours and the introduction of a decision support system to help clinicians see what test needs ordering depending on what drug they want to prescribe.

He said often, it's not the dose that matters, but the exposure (the amount of drug that gets into the system) and gave the example of warfarin. 1% of the UK population take warfarin with wide dose variation and the individual daily dose requirement is influenced by many factors. Taking all of these factors into consideration, an algorithm had been developed which was then tested in a randomised controlled trial. In those who had been genotyped and used guided dosing, patients were in a therapeutic range 67% of the time versus those in the control arm of standard dosing being in range 60% of the time. This was a statistically significant difference and was cost effective and comprised a simple cheap genetic test (a mouth swab sent for test of 2 genes, taking 45mins and costing £10). He said improvement of dosing in warfarin based on these tests done by nurses could save the NHS £500 million per year as opposed to putting patients on the new oral anticoagulants which cost the NHS £1 billion a year.

He described some anaesthetic issues saying that patients will start presenting for anaesthesia with their genetic test results, knowing that they have conditions such as atypical pseudocholinesterase and with specific information about the variant that they have. He also talked about how work is being done in Leeds on malignant hyperthermia and mutations in the ryanodine receptor.

He spoke about genotyping for pain therapy and specifically the CYP450 2D6 gene which is responsible for metabolising 25% of drugs in the BNF. He said 8% of the population are poor metabolisers and 2% are ultra rapid metabolisers. He gave the example of codeine and said that those who are poor metabolisers lack the enzyme, therefore the drug is not efficacious, as opposed to the ultra rapid metabolisers who may suffer with codeine induced respiratory depression.

He ended by saying we are producing vast amounts of big data and the pace of accumulation accelerating, driving forward gene therapy. However, we need people in the NHS who can interpret and analyse this data so that it can be used to the advantage of patients.

Prof. Pirmohammed took questions from the floor and the vote of thanks was given by Dr Neil Mercer.

Dr Gemma Roberts
Honorary Secretary, LSA