PERSONALIZED MEDICINE – ARE WE THERE YET?

HIGHLIGHTS FROM THE SOCIETY OF MEDICINES RESEARCH SYMPOSIUM, HELD OCTOBER 2, 2014 – NATIONAL HEART & LUNG INSTITUTE, KENSINGTON, LONDON, UK

R.J. Anderson[1], F. Fallah-Arani[2], P. Jeffrey[3], M. Konneh[4] and R. Lock[5]

[1]University of Sunderland, Sunderland; [2]UCB, Berkshire; [3]Pfizer Ltd., Cambridge; [4]Biotrial International Ltd., London; [5]Takeda Development Centre Europe Ltd., London, UK

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SUMMARY

The Society for Medicines Research Symposium, sponsored by Biotrial International Ltd and Pharmidex, was held at the National Heart and Lung Institute, Kensington, London, UK. The meeting focussed on the current UK efforts and progress around the promise of personalized medicine in improving the diagnosis and prognosis for patient care. From theory to practice; experts from academia, industry and UK strategy groups highlighted the commitment and progress underway in this exciting and developing field.

Key words: Personalized medicine – Stratified medicine – Human genome – Precision medicine – Genomic medicine

PERSONALIZED MEDICINE

The first decade of the 21st century saw the sequencing of the human genome and brought with it the promise of transforming our understanding of health and disease and revolutionizing our approach to general medicine. Coupled with the explosion of 'omics-based technology and data analysis capabilities, healthcare scientists are now able to measure and quantify drug activity at every biological level. The integration of these vast data sets combined with appropriate clinical data from individual patients has the potential to improve patient care by adopting more efficient treatment paradigms tailored to the individual, rather than just the clinical diagnosis. But with the promise brings challenges, including redefinition of current approaches to patient privacy and confidentiality, reimbursement policies and regulatory oversight, in order to accommodate the changes personalized medicine will bring to healthcare.

PERSONALIZED/STRATIFIED MEDICINE: NEW HORIZONS FOR THE PHARMACEUTICAL INDUSTRY..... AND PATIENTS

Professor Trevor Jones (Director Allergan and former Director General of the Association of the British Pharmaceutical Industry 1994-2004) opened the meeting with his thought-provoking and challenging talk "Personalised/stratified medicine...new horizons for the pharmaceutical industry...and patients". Historically, diseases and deaths were described symptomatically, as illustrated by the Bills of Mortality that originated in London in the early 16th century. However, during the last century more precise descriptions based on the underlying pathophysiology have emerged. In turn, our understanding of the causes of disease and the resulting treatment and therapies are now further developing based on genomic and epigenomic data coupled with the improvement and expansion of analyt-

ical technologies. On the plus side these advances generate ever increasing volumes of data relating to biological mechanisms and patient behaviors, thereby aiding our fundamental understanding of diagnosis and the prescription of the optimal therapy, while on the downside our capability in data handing and analysis techniques is becoming rate limiting.

The use of biomarkers across the entire drug discovery and drug development landscape, from the early preclinical phase to late-phase clinical studies has also increased dramatically. Despite widespread use in determining target engagement and clinical efficacy, there are relatively few companion diagnostics approved by the US and European regulatory authorities. The changing business model in the pharmaceutical industry from "blockbuster" drugs prescribed to broad segments of the population to the more targeted "niche-buster" drugs aimed at smaller, more segmented and better-defined populations calls for greater investment in diagnostic tools. Such investment requires a paradigm shift in the way researchers, prescribers and payers think about personalized and/or stratified medicine. In the UK alone, the Medical Research Council (MRC) focus for the coming years will see major investment in several key initiatives. The Farr Institute for Health Informatics is a UK-wide institute, coordinated by the MRC, linking research activities in 19 universities supported by more than GBP 35 million worth of funding. A further GBP 2 million is committed to support a UK Health Informatics Research Network to tackle the issues of methods development, training and public engagement and funding from the MRC of GBP 32 million to continue to improve the UK capability, capacity and capital infrastructure in medical bioinformatics represents significant long-term commitment to this field (1).

Innovative medical technology is being developed to provide wearable monitoring devices with real-time feedback mechanisms to generate data on patient compliance and drug efficacy. Google and Novartis' Alcon eye division recently announced a collaboration to develop a smart contact lens that monitors blood-sugar levels and will enable patients to manage their own health, thus potentially lowering the cost of managing chronic diabetes. There are a growing number of wearable technology and software products used to monitor health and fitness with Google (Google Fit) and Apple (Healthkit) having products already available. However, all this data and information is not without risk and the role of the Genetic Counsellor is becoming more important as our diagnostic capability increases. Counseling is a complex process covering both diagnostic (the actual estimation of risk) and supportive aspects by which patients or relatives at risk of an inherited disorder are advised of the consequences and nature of the disorder, the probability of developing or transmitting it, and the options open to them in management and family planning.

In concluding, Professor Jones highlighted the significant progress that the scientific community has made, but in doing so we have perhaps generated more questions than we have answers and there is still much work to do.

GENOMIC MEDICINE – TIME FOR TRANSLATION

Dr. Tom Fowler (Genomics England) gave an overview of the work of Genomics England, a group set up to deliver the UK government's strategy on sequencing 100,000 whole genomes, in his talk 'Genomic Medicine – Time for translation'. Genomic England's aim is to sequence 100,000 whole genome in NHS patients with a rare inherited disease. These include rare cancers and pathogens, with the potential of generating health and wealth benefits whilst leaving an infrastructure legacy, developing human capital and securing domain expertise for England in a quest to become world leader in genomic medicine.

About 3 million people in the UK have inherited rare diseases, about 5% of the population. There are 7,000 rare disorders—often disabling and very costly. Around 85% of these have a single gene defect. Early knowledge of disease carriers may avoid disability in the long term. Whole genome sequencing (WGS) increases the discovery of gene defects by about 25%.

In rare diseases, Genomics England is working with a number of partners, including the NIHR Translational Research Collaborative in Rare Disease where extensive and in-depth phenotyping is being conducted, an essential part of understanding the relationship between gene sequence and disease manifestation. There is also the NIHR Bioresource in rare diseases, investigating 12,000 whole genome sequences.

Dr. Fowler described several disease areas where there was potential for therapeutic innovation, mostly in diseases where there is a loss of function, usually recessive disorders, a notable example being cystic fibrosis—where there is an alteration in protein activity, requiring an intervention of chaperonin therapy. Cancer is the prime example of a disease of disordered genomes and a disease where various bodies have been active in applying a WGS strategy to better understand the genetic basis of the disease and develop specific therapies. Together, the CRUK Stratified Medicine/Leukaemia consortia/NIHR BRCs are exploring the feasibility of creating a comprehensive catalogue of cancer genes. Recent analysis indicates that larger sample sizes will reveal many more genes mutated at clinically important frequencies.

With phase I of the Genomics England study completed, phase IIa has been investigating 2,000 rare diseases through WGS during 2014. Phase IIb will investigate 3,000 cancers by WGS; phase III will follow in 2015-2017. The data generated by this study will be owned by Genomics England, but will be available for use by academics, clinicians, and industry, in recognition that such partnerships are necessary to promote development of diagnostics and therapies for personalized medicine.

PERSONALIZED MEDICINE – THE TECHNOLOGY STRATEGY BOARD'S PERSPECTIVE

Dr. Penny Wilson provided insight into the role of Innovate UK (previously TSB – Technology Strategy Board) in encouraging and supporting innovation across many sectors of UK industry, by bringing together researchers and industry to collaborate on new products and new technologies. Healthcare is a priority area, with GBP 55 million funding in this financial year. The 'one size fits all' approach to prescribing does not meet the needs of all patients and there are many patients who do not respond to their treatment: non-response to angiotensin-converting enzyme (ACE) inhibitors is 10-30%, to β-blockers 15-25%, to statins 30-70%, to antidepressants 20-50% and to β_2-adrenoceptor agonists 40-70%. To what extent non-response

is due to non-compliance is unclear, but the need for personalized medicine is evident: the right therapy at the right dose, to the right patient at the right time, leads to improved outcomes, fewer complications, better use of finite resources and the most effective use of medicines. However, to deliver in this arena will require an increased understanding of disease pathology, improved diagnostics and the design of more selective therapies.

Accepting that there are bioinformatics challenges, it is estimated that an individual's entire genome could be sequenced in about 30 minutes by 2019-2020. However, there remain questions, such as 'what will be the clinical application of such tests', 'how will it help', and 'what are the incentives to the adoption of stratified medicine'? The stratified medicines innovation platform (SMIP) is designed to support the development of knowledge and technology that will lead to greater access to appropriate stratified medicines and suitable diagnostics for their wide adoption. SMIP aims to maximize the potential of Stratified Medicine in the UK and works with industry, academia, government and the third sector. For example, SMIP support for the development and validation of a test by Almac Diagnostics to direct FEC (5-fluorouracil, epirubicin and cyclophosphamide) treatment to those breast cancer patients who are most likely to respond to this cocktail may benefit up to 17,400 UK patients annually (2).

Innovate UK recently created a series of 'Catapult' centers across the UK, which are part of a world-leading network of technology and innovation centers, aiming to bridge the gap between business, academia, research and government. These centers attract long-term investment to transform the UK's ability to create new products and services, opening up global opportunities for the UK and generating sustained economic growth for the future.

The Precision Medicine Catapult aims to grow the precision medicine industry by providing the technological infrastructure, expertise and connections for the development of precision medicine products. It aims to address two of the barriers to precision medicine: the slow commercialization and high risk attached to new tests, and the difficulties with combining diagnostics and therapy, which currently challenge precision medicine clinical studies. The new center will decrease the risk and costs of new precision medicine tests by offering access to development and validation labs, and facilitate precision medicine clinical trials by creating a clinical trial system of 30-40 hospitals focused on precision medicine, alongside a dedicated pathology laboratory service. Targeting cancers, infection and inflammatory conditions, this approach is likely to have significant real-world impact within 10 years.

PERSONALIZED MEDICINE – AN INDUSTRY PERSPECTIVE

Dr. Farhat Syed (GlaxoSmithKline) offered insight into the industrial opportunities and challenges presented by stratified medicine in her presentation entitled 'Personalised Medicine – An Industry Perspective', focusing on Immuno-Inflammation (II). Implementing a strategy of finding the right therapy for the right patient population has been challenging in II due to the complex interplay of mechanisms driving disease pathogenesis, as well as difficulty in accessing tissues at sites of disease.

Stratified medicine in II conditions has been largely driven by the patient's response to treatment—either non-response or adverse effects. Trends towards using molecular biomarkers to stratify patients with a specific mechanism to improve drug efficacy are being currently tested clinically. Dr. Syed then highlighted the benefit of taking this approach with some examples.

In the case of Benlysta (belimumab), an anti-BlyS monoclonal antibody (mAb), a retrospective analysis of the failed phase II clinical trial data identified a subgroup of patients with active systemic lupus erythematosus for whom this treatment was indeed effective (3).

Another example was highlighted from the field of asthma where the review of clinical trial data from the DREAM trial, using mepolizumab, an anti-IL-5 mAb, identified another subset of patients who responded well to this treatment (4).

Overall in the field of II, stratification is not sufficiently early and there are many opportunities to improve treatment, while robust collections of clinical biomarker data will help to enable decision making. Drivers for these changes are improved efficacy of treatment, avoiding exposing patients to unnecessary risk with no clear benefit, reduced attrition, through identifying homogeneous patient populations for clinical trials and clinical applications, and reimbursable file, supported by clear efficacy and benefit.

STRATIFIED MEDICINE – A CANCER RESEARCH UK PERSPECTIVE

Dr. Ian Walker explained how the personalized medicine agenda has been greatly informed by recent advances in cancer research and treatment, driven largely by technological advances leading to greater understanding of cancer biology and the need for better patient outcomes through new and existing treatments. These developments are starting to enable the stratification of patients, not only by type of cancer, but down to the detail of receptor and protein expression to target specific and effective therapy.

Cancer Research UK (CRUK) dedicated over GBP 350 million to research during 2013/14 in the UK, involving ca. 5,000 scientists working on all types of cancer, making it the biggest medical research charity worldwide. With research spread across about 40 cities and towns in the UK and an extensive network of research institutes, centers, and clinical trials units, alongside the development of new collaborative models for cancer research (5), CRUK provides a unique opportunity to approach the treatment of cancers in a new way.

In 2011, a partnership was established between CRUK, TSB (now Innovate UK), and a number of industrial members, such as Pfizer and AstraZeneca, to a stratified medicine pilot program to which 9,000 patients were recruited across the CRUK network. Almost 40,000 gene tests were carried out to identify the incidence of specific markers known to be linked to six tumor types (Table I).

The initial findings highlighted some differences between the tested tumor types, with distinctively dissimilar results for each. For example, of the 1,899 lung cancer samples tested for the 5 aberrations listed in Table I, more than 60% reported with no genetic aberration, while 35% showed at least 1 mutation across the genes tested, but only 0.65% showed the presence of more than 1 mutation. *KRAS* was the most frequently mutated gene (26%), followed by *EGFR* (8.3%), *ALK* rearrangement (1.9%) and *BRAF* (1%). In contrast, of the

Table I. *Testing carried out for a range of markers over six tumor types.*

Colorectal	Lung	Breast	Prostate	Ovarian	Melanoma
BRAF	EML4 ALK	BRAF	BRAF	BRAF	BRAF
KRAS	BRAF	TP53	TMPRSS2-ERG	TP53	KIT
NRAS	EGFR	PIK3CA	PTEN	PTEN	NRAS
PIK3CA	KRAS	PTEN			PIK3CA
TP53	DDR2				

1,634 colorectal cancer samples tested, the incidence of aberration negative results was about 20%. Overall, 47% of CRC samples showed one mutation, > 30% had two mutations, and almost 3% had three mutations, with *TP53* being the most commonly mutated gene (> 50%), both as a single mutation and in combination with another, and *KRAS* mutations also highly represented across singly and multiply mutated genes (ca. 40%). Of course these data reflect the nature of using a limited gene panel approach (6).

Although > 98% of patients consented to their tissue and data being used, the study highlighted the need for routine consent to allow research using tissue and data. Other challenges to the operational delivery of a stratified medicine approach were identified, such as the crucial importance of a suitable quality assurance system; the critical role of pathology departments in the management of tissue samples and the need for standards for sample handling, preparation and processing to be established; the huge number of tests being run across the three CRUK technology hubs; and the consequent challenges of delivering clinically relevant turnaround times.

A new CRUK stratified medicine program is now under development, through an academic, government, industrial partnership that aims to stratify the treatment of lung cancer on a national scale. Compared to many other cancers, such as breast and bowel cancer, survival rates for lung cancer have not improved significantly over the last 40 years. The National Lung Matrix Trial will be a phase IIa signal finding study with no randomization, carried out under a single clinical trial protocol and regulatory submission. Rather than all lung cancer patients receiving the same standard therapy, they will be stratified into different treatment groups according to specific biomarkers, such as *EGFR/ALK* gene status. The next-generation screening (NGS) technology will be provided by Illumina, identifying multiple types of genetic aberration; subsequently, the diagnostic results will direct patients' treatment with drugs in development, appropriate to their biomarker status. The program will be delivered in two stages: firstly through high volume molecular prescreening, looking to test approximately 2,000 non-small cell lung cancer (NSCLC) patients per year, and then utilizing the extensive CRUK network to manage the multiple stratified arms of the clinical trial, to which the stratified patients will be recruited, providing cohorts of patients with tumors sharing common aberrations and a multi-armed nationwide matrix study, in which every center has access to all arms and delivers the right drug to the right place for the right patient. The trial will be delivered through the CRUK Clinical Trials Unit in Birmingham and chief investigator Professor Gary Middleton.

This new model has advantages for patients, sponsors and the pharmaceutical industry: shared costs for quicker trials that are easier for patients, requiring fewer re-biopsies and also including rare mutations. It will change the way we develop stratified medicines within the UK and provide greater options for patients with lung cancer.

HER2 AS AN EXAMPLE OF PERSONALIZED HEALTHCARE

Dr. Graham Ross (Roche) gave a comprehensive overview of the use of prognostic biomarkers in aid of personalized healthcare. He based his talk around the example of HER2 receptor and its role in a variety of tumor types. In malignant cells, overexpression of HER2 has been shown to be a major driver of the malignant process (7) and in certain types of tumors, particularly breast cancer and gastric cancer, this overexpression is associated with a relatively poor outcome. HER2 is therefore a reliable negative prognostic marker. However, measurement of HER2 is complex and requires stringent quality control.

Dr. Ross then highlighted the successes in HER2 as a targeted therapy with the examples of antibodies such as pertuzumab and trastuzumab. The latter, when added on to therapeutic regimens in metastatic or early HER2-positive breast cancer patients, has improved outcomes (8). Furthermore, it has improved survival in HER2-positive gastric cancer patients, therefore, confirming that HER2 positivity is a predictive biomarker for response to targeted HER2 therapies and its use has improved prognosis and added value to patients' lives.

PERSONALIZED, STRATIFIED OR PRECISION MEDICINE, A VIEW FROM THE WOLFSON CENTRE FOR PERSONALIZED MEDICINE

Dr. Ana Alfirevic presented an insight into the approach that has been taken by the Wolfson Centre for Personalised Medicine (WCPM) in her talk entitled 'Personalised, stratified or precision medicine, a view from the Wolfson Centre in Liverpool'. She highlighted that pharmacogenomics is used to find biomarkers for drug efficacy and toxicity; however, the uptake of genetics into clinical practice is currently still slow. The WCPM is prominent in utilizing pharmacogenetic testing in the clinic, which includes the generation of evidence based on observational studies, randomized control trials and meta-synthesis.

Dr. Alfirevic then discussed some examples from the field of drug-induced hypersensitivity where pretreatment genetic testing for HLA alleles can reduce the rate of adverse drug reactions. The best example is abacavir, an antiretroviral drug that causes hypersensitivity in approximately 9% of patients, for which an association with HLA-B*57:01 was found. The example of carbamazepine, an anticonvul-

sion and mood-stabilizing drug, was also discussed; it can lead to severe reactions, such as Stevens Johnson syndrome, found to be strongly linked to HLA-B*15:02 in a mainly Asian population. In Caucasian and Japanese patients, however, carbamazepine hypersensitivity is associated with HLA-A*31:01.

One of the challenges is the currently inappropriate interpretation of the vast amount of data generated through pharmacogenomics. Therefore, significant efforts at the WCPM are also committed to the education of clinicians and scientists and to patient and public engagement to promote personalized medicine.

DRIVING PERSONALIZED MEDICINE IN RARE DISEASE AND CANCER THROUGH GENOMICS

Dr. Jenny Taylor (Wellcome Trust Centre for Human Genetics, University of Oxford and Oxford NIHR Biomedical Research Centre) delivered a talk on ''Driving personalised medicine in rare disease and cancer through genomics''. NGS technologies are revolutionizing genetic diagnostics; since 2012, tumor gene profiling in Oxford has progressed from a few single gene tests, such as *EGFR*, *KRAS* and *BRAF*, through 5-day multiplex 50-gene hotspot tests, with 150 gene custom tests being evaluated. Clinical WGS is being piloted locally and will be offered imminently at a national level by Genomics England, providing a molecular diagnosis for the conditions of more patients.

For cancer, the profile of a patient's tumor according to clinically actionable mutations, linked to the pathology, can inform appropriate selection of a particular targeted molecular therapy, providing personalized molecularly targeted cancer treatment, or can allow stratification of patients into an appropriate clinical trial for their particular tumor type. In Oxford, a 50-gene NGS panel has been validated against standard clinical tests and cost effectiveness has been evaluated. Of > 1,500 patients tested by Oxford in 2013-2014, a substantial number experienced a change in their disease management as a result, either as part of clinical management or entry into trials.

WGS will increasingly be applied to clinical patients. In an early pilot study on clinical lymphocytic leukemia, detection of emerging mutations was possible months before clinical relapse (9), although available drugs limited consequent clinical decisions that could be taken.

In an attempt to assess the clinical utility of WGS more broadly, Oxford set up its WGS500 study to sequence 500 genomes across a wide range of diseases, a collaboration which involved a network of 35 academic clinicians and scientists with expertise in rare diseases, immunological disorders and cancers. The impacts of this are diverse and include discovery of novel disease genes (10, 11), new clinical diagnoses with concomitant impact on clinical management of patients, and new targets for routine diagnostic testing.

Future work to deliver on personalized medicine will now involve integration of genomics and other 'omics with molecular pathology to provide a more comprehensive profiling of cancers for personalized medicine.

DISCLOSURES

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