FEAM Conference 2018
on Precision Medicine and Personalized Health

Friday, 28 September 2018
Campus Biotech, Geneva, Switzerland

Hosted by the Swiss Academy of Medical Sciences

Summary report

SAMW ASSM
Schweizerische Akademie der Medizinischen Wissenschaften
Académie Suisse des Sciences Médicales
Accademia Svizzera delle Scienze Mediche
Swiss Academy of Medical Sciences

FEAM
Federation of European Academies of Medicine

Disclaimer
Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Federation of European Academies of Medicine (FEAM), the Swiss Academy of Medical Sciences (SAMS) and their members.

All web references were accessed in December 2018.

Acknowledgments
We warmly thank speakers and chairs for their contribution, Catherine Collins for writing this report and the Swiss Academy of Medical Sciences (SAMS) for hosting the conference.

The Federation of European Academies of Medicine Conference 2018 on Precision Medicine and Personalised Health

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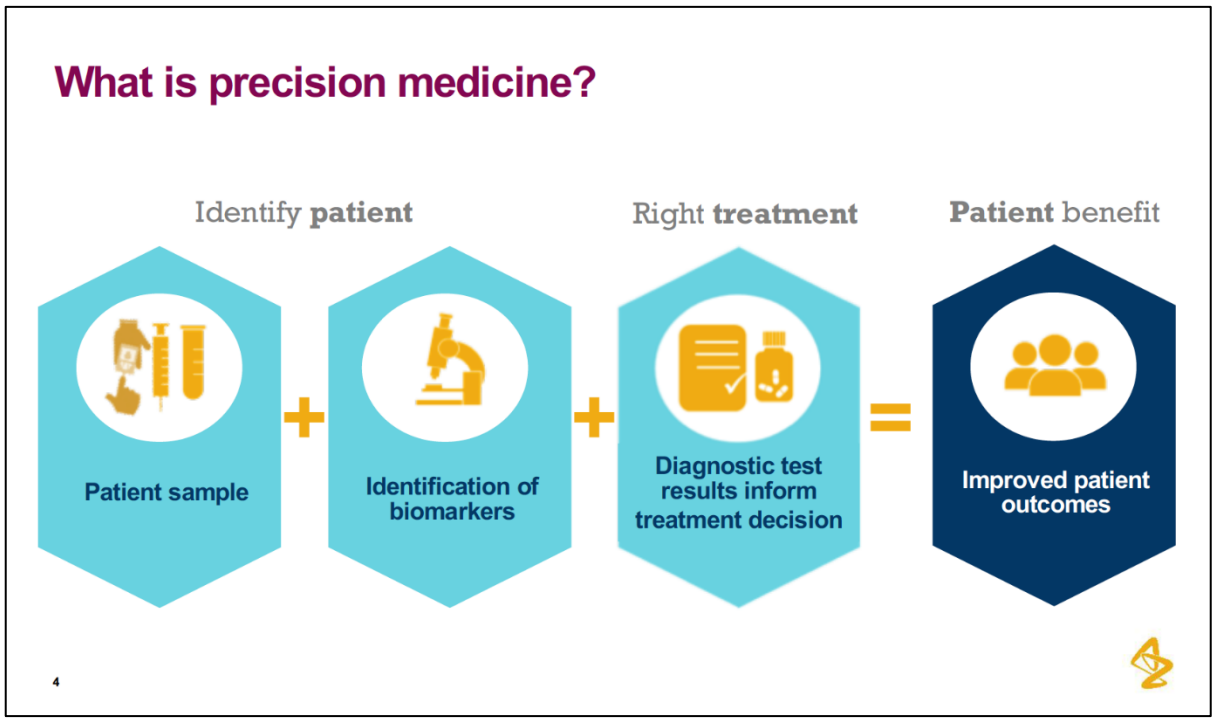


Courtesy of Dr Thorsten S. Gutjahr, Vice President of the Global Head of Companion Diagnostics, Astra Zeneca

The FEAM Conference on Precision Medicine and Personalised Health 2018 took place on 28 September at the Campus Biotech Geneva, Switzerland, and was hosted by the Swiss Academy of Medical Sciences.

Personalised medicine has captured the attention of the media and the public alike, as ever more research emerges and new technologies appear on the market. Fitness apps and diet trackers with in-built health monitors are becoming increasingly popular, the general public is becoming more and more health literate, and people are fascinated by new health technologies and developments, especially in the field of personalised health.

Although personalised treatment is perceived as a new field of medicine, Prof. George Griffin, President of FEAM, pointed out in his opening speech at the FEAM Conference on Precision Medicine and Personalised Health 2018 that doctors have in fact been practising personalised medicine for centuries, evaluating each individual patient based on their personal symptoms, their unique circumstances and family history. Prof. Griffin wondered whether personalised medicine is the right term to use, after all, for this new field? He also looked to the way artificial intelligence is changing medicine, referring to a colleague of his, a soon-to-be retired radiologist, who was very happy to be nearing the end of his career as it seemed inevitable that machines would take over his job.

'The goal is to make health data and molecular data available for research but also for patient care. The data should be shared among all hospitals and physicians,' he said.

Prof. Daniel Scheidegger, the President of the Swiss Academy of Medical Sciences (SAMS) spoke about the importance of considering the investments made in personalised health

carefully, to ensure that they are sustainable. He mentioned the dangers of personalised health becoming viewed as just the latest major income source for the pharma industry.

Prof. Ron van Schaik, President of the European Society of Pharmacogenomics and Personalised Therapy (ESPT), then spoke about the 4th ESPT Summer School, which involved 80 participants from 26 countries. The summer school consisted of 4 full-day meetings, 6 student workshops and 40 plenary lectures in a genomic facility. There was a broad mix of people from very different disciplines, he said, and he promoted the next ESPT summer school, which will be held in Seville, Spain, October 16-19, 2019.

Next, Prof. Peter J. Meier-Abt reported on the FEAM forum expert round table discussions. The main conclusions were: a good test is as important as a good drug; it's important to find the right biomarkers and the right patient for a specific treatment.

The experts shared knowledge on existing initiatives, made suggestions for the implementation of companion diagnostics in daily practice, and discussed current regulatory barriers. The role of physicians was also debated – specifically, how physicians have to become mediators between companion diagnostics and precision medicine and have to advise the patient very carefully. The whole procedure can create anxiety in the patient, and anxiety management must be learned. Precision medicine must have a patient-centred approach that should go hand-in-hand with companion diagnostics. There should also be a reimbursement scheme so that everyone can afford these new therapies, according to the experts. 'We should keep in mind that the patient at the end is the most important issue,' said Prof. Meier-Abt.

The experts at the FEAM Conference on Precision Medicine and Personalised Health included practicing doctors, academic researchers, industrial scientists, lawyers and an ethicist. The spread of disciplines and backgrounds gave the audience a wholistic view of the progress and the potential issues and problems that are arising in relation to personalised health. What are the medical developments? Will the personalised medicine field be dominated by tech companies? How will the field be regulated? What are the implications of GDPR? How will citizens receive personalised health services? What are the ethical questions that need to be raised? These questions and more were tabled during the discussions, and the summary of the conference can be found here.

Breakthrough Science and New Developments

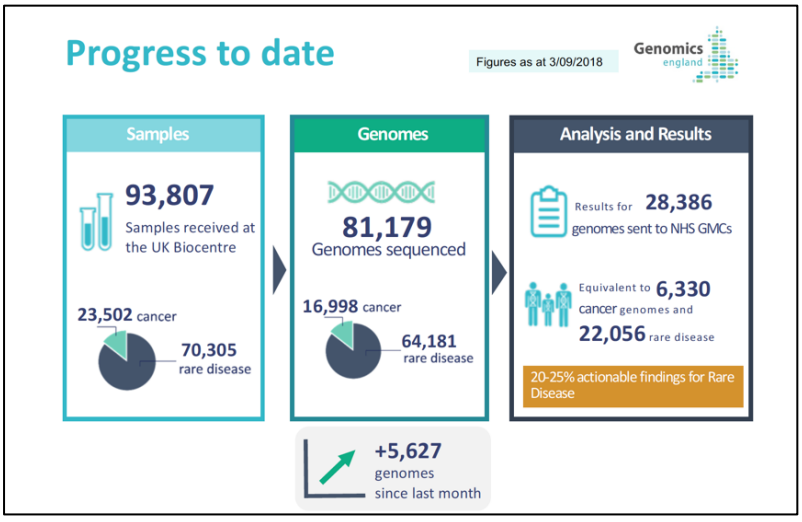
1. The 100,000 Genome Project
Presented by Prof. Tim Hubbard, professor of Bioinformatics at King's College London, Head of Genome Analysis at Genomics England and Honorary Faculty at the Wellcome Trust Sanger Institute in Cambridge, United Kingdom

The mission of the 100,000 Genome Project is to enable large-scale genomics research and to improve the health of individual NHS patients. Participants are referred by their doctors to receive genetic information relating to their problem, and can then 'opt-in' to find out whether they have 'serious and actionable' conditions or are carriers for rare diseases. The whole genome is sequenced, and the results inform patients about their genetic risk for cancers in various organs including lung, breast, ovarian, prostrate, colorectal, renal, testicular, head-and-neck, and skin.

The mission of the project is to improve the health of patients, but also to create a legacy of infrastructure, human capacity and capability in the British NHS (National Health Service), stimulate wealth generation in the economy and enable large scale genomics research.

There are currently 13 Genomic Medical Centres across the UK. Patients give their consent to be a part of the project at these centres, then their DNA is sequenced by Illumina, an external company. Genomics England, the organisation coordinating the 100,000 Genome Project, also engages Genome Interpretation Services Companies. The data is then stored and analysed in data centres and clinical interpretation centres.

Patients generally receive information about their main condition, optional information about additional 'serious and actionable' conditions and whether they have carrier status for certain rare diseases.



As a result of the 100,000 Genome Project, breakthrough developments were made in TB. Researchers found that they could isolate different strains of TB using genome sequencing, which meant that patients who could have waited months to receive the right treatment can be diagnosed in days – maximising their chances of recovery.

Prof. Hubbard then presented the Genomics England Clinical Interpretation Partnership (GeCIP), a research partnership designed to accelerate partnerships between academics and industry to faster develop diagnostics and therapies.

Diagnosis success rates

Genomics england

Rare:

- Current clinical genetics services:
  - Single gene tests, panels: 15-20% diagnosed
- 100,000 genomes project:
  - Whole Genome sequence: Another ~25% diagnosed

Cancer:

- No existing systematic cancer genetics service in NHS
- 100,000 genomes project:
  - Whole Genome sequence: ~60% of reports identify variants in "actionable genes"

He discussed how the project had addressed GDPR, and showed the conference the #DataSavesLives website, which educates patients about the use of their data by universities, researchers and hospitals. Engaging with the public about the use of their data is vital to gain patient support for genome research.

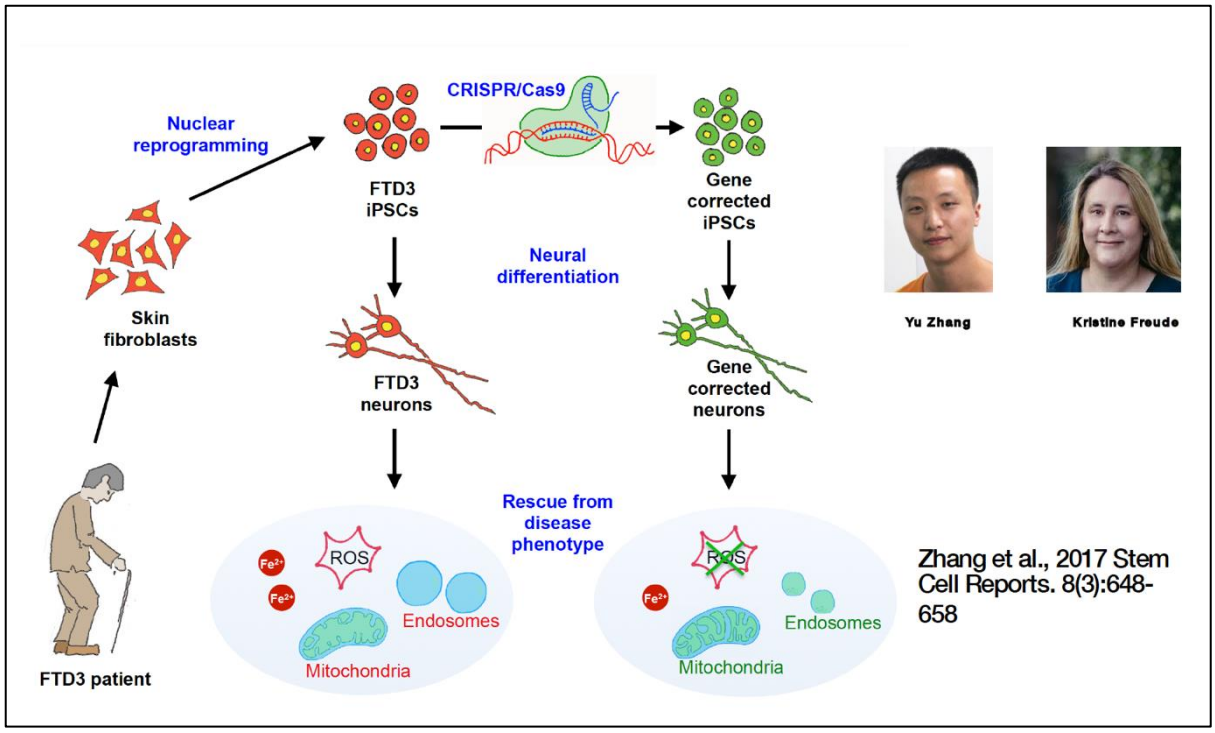
2. ***Towards Personalised Regenerative Cell Therapy***
   Presented by Prof. Yonglun Luo, Department of Biomedicine, Aarhus University Denmark and Lars Bolund Institute of Regenerative Medicine, BGI-Qingdao, China.

Dr Yonglun Luo opened his talk by remarking how even before we are born, a lot can go wrong. And as we age, things only get worse. The incidence of both degenerative diseases and cancers increase with age, he noted, and said that 'after his talk, many cells in his body would have been mutated.'

But with DNA sequencing, we can identify what already went wrong, predict what will go wrong, select the best treatment and then design the most effective solution (precision medicine). The image on the left shows DNA sequencing machines.

After that, comes genome engineering. This involves precision positioning, cleavage and modification. The CRISPR CAS-9 system is used by the bactericidal permeability increasing protein (BPI).

The next step is stem cell engineering, the so-called regeneration stage. Mesenchymal stem cells are highly important for regeneration. These can be found in adult tissues and fetal tissues alike. MSCs can also be derived from pluripotent stem cells. This will lead towards personalised regenerative cell therapy.



The replacement stage has been achieved using animal biotechnology. Human cells can be injected into blastocysts derived from animals that are deficient in a pancreas, for example. A human pancreas is then produced within a livestock animal (such as a pig). This pancreas can then be used for human organ transplantation.

3. *Breakthroughs in oncology*

Presented by Prof. Christophe Le Tourneau of the Intitut Curie, Paris & Saint-Cloud, and head of the Drug Development and Innovation Department INSERM U900 Research unit, Versailles Saint-Quentin-en-Yvelines University, France

Prof. Christophe Le Tourneau explained that personalised medicine can be especially useful when a patient is in the metastases phase of cancer, but that it is not useful where a simple tumour is present.

Sequencing can be used to determine whether breast cancer patients will need chemotherapy or not, for example.

Personalised medicine can determine treatment routes for metastatic cancer

However, Prof. Le Tourneau emphasised that there remain still big challenges – as an example he mentioned bioinformatic pipelines, where results are critically dependent on the pipelines used. As bioinformatic pipelines are used to run sequencing, this can be problematic.

Molecular alterations might be relevant in the future for certain cancer types. However, it's likely that one single molecule will not be sufficient, but the whole molecular landscape will be more significant. According to Prof Le Tourneau, sequencing has been shown to successfully determine whether breast cancer will need chemotherapy or not, and that all recurrent or metastatic cancer patients should be sequenced for microsatellite instability (MSI) and Novel Targets for Tumor-Agnostic Cancer Therapy (NTRK) fusions, and potential inclusion into clinical trials. However, the predictive value of sequencing to guide therapy in cancer patients has not yet been demonstrated.

4. *Genomics and Big Data*

Presented by Prof. Stylianos Antonarakis of the Department of Genetic Medicine and Development at the University of Geneva, Switzerland

Prof. Antonarakis first gave an overview of genetics, stating that every time DNA is copied, some mistakes are made, and that these mistakes can accumulate over time. He then spoke about human genomes, highlighting that every person is different – but not, genetically speaking, by much. Individual human genomes are 99.1% identical he said, and all of our individual differences are caused by the remaining 0.9%. Genomic variability provides the opportunity to evolve and adapt, but of course there is the obvious drawback – genetic disorders.

Individual human genomes are 99.1% identical

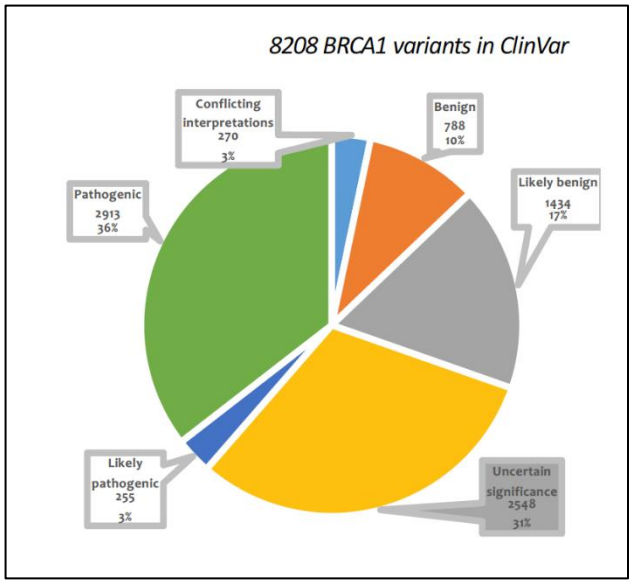
Prof. Antonarakis elaborated on big data and genomics: "For the general physician and lay people, big data starts with the genomes. Big data for the lay public and the physician is a vast sea of data that you cannot analyse or look at with your naked eye or unprepared brain. You need a machine that can analyse this data," he said. Prof. Antonarakis then brought out a book which describes the nucleotide sequences of human chromosome 21, typed out in font size 6. The book is a hefty tome!

Precision medicine, he said, is medicine based on genetic variation, whereas genomic medicine is medicine based on the genetic variation of an individual.

"Genomic medicine is not new. We've been practicing it since the beginning of the 20th century. In every hospital when we do blood transfusion, we perform genomic medicine. Because we match a window of variation between the donor and the recipient," he said.

The medical genome refers to the 0.3% of the genome that contains approximately 4000 protein-coding genes. There are also 1600 protein-coding genes not yet linked to Mendelian disorders.

He then discussed several case studies – a six-year-old with developmental delay and a twelve-year-old with extreme developmental delay. The six-year-old was found to have a benign variant of the DYRK1A Thr356Ala heterozygote whereas the twelve-year-old had a pathogenic variant.



Prof. Antonarakis then spoke about the problem of Variants of Unknown Significance, or VUS. According to a 2015 study in the UK, 39% of breast cancer specialists did not know how to explain VUS to a patient with no family history, and 71% were unsure about the clinical implications of the test reports.

5. Precision medicine and the metabolome
Presented by Prof. Amalio Telenti, Department of Integrative Structural and Computational Biology of the Scripps Research Institute, La Jolla, United States of America

Metabolomics is the study of low molecular weight molecules or metabolites found within cells and biological systems. Prof. Telenti described the metabolome profile as a trait of an individual, and said that there are a lot of rare variants in the general population that are still not mapped, and these variants can have a significant effect on unique metabolites, with unclear health consequences. Approximately 10% of the global population carry rare variants that influence the metabolome. In some ways, Prof. Telenti said, metabolomics is the new pharmacogenetics.

Body mass index, or BMI, alters about 30% of metabolites in the human body. Every single kilo affects the metabolites within our system. Doctors now know, however, that people can have a normal weight, a healthy BMI, but an unhealthy metabolome. This can increase the risk of developing diseases like diabetes or heart failure. Likewise, obese people can have a healthy metabolome that could decrease their risk of diabetes and heart disease, despite their weight.

Metabolome analyses can, therefore, generate rich biomarkers. It is an agile system that can track responses to intervention or treatment. It can summarise in one single analysis multiple tests that are part of a medical routine, therefore speeding up diagnosis.

Metabolomics may help to understand better the mechanisms of action as well as the toxicity of medications, as drugs can also generate metabolome signatures according to Prof. Teleni.

His research showed that the use of acetaminophen impacts the sulfonation of sex hormones, but researchers have not yet determined whether this is a good or a bad thing. When people take paracetamol, their usually sulphated sex hormones will not be sulphated.

Older by 30 years?

'Is that good? I have no clue,' said Prof. Telenti. The impact during pregnancy in particular could be important, and further research is needed to determine this. Interestingly, a single dose of acetaminophen ages people by thirty years (metabolically speaking) for the day that they are taking the dose.

6. Personalised Lipid-Lowering Therapy
Presented by Prof. Jan Albert Kuivenhoven, Department of Pediatrics, Section Molecular Genetics at the University Medical Center Groningen, the Netherlands.

Cardiovascular diseases are affected by interactions between lipids within the body. 17.8 million people die every year from cardiovascular disease throughout the world.

Generally speaking, plaques begin to build up in your arteries from childhood onwards, but they are only treated when clinical events have occurred at a cost of about €60 per year (statins).

There are two forms of cholesterol found within the blood, HDL cholesterol which is high density lipoprotein cholesterol, the so-called "good" cholesterol, and LDL cholesterol, low-density lipoprotein cholesterol which contributes to heart attacks, strokes and heart disease.

LDL cholesterol levels tend to increase with age but the patterns by which it increases differs according to gender. LDL cholesterol increases rapidly in men from the age of 20 onwards but in women, it only starts to increase after the menopause.

One in every 250 people have high cholesterol due to genetics

There are some people that have naturally high levels of cholesterol. About one in every 250 people have familial hypercholesterolemia (FH), so 7.7ml of cholesterol per litre of blood.

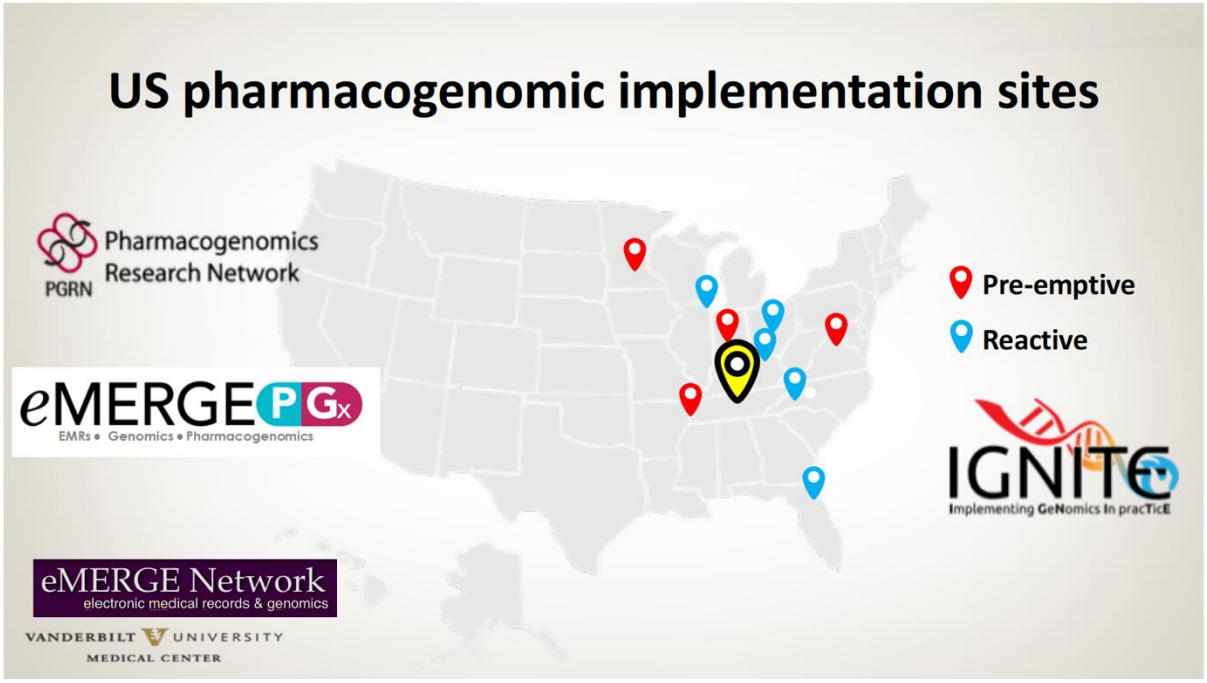
"You don't want to be one of these people," said Prof. Kuivenhoven. People with FH have to start taking statins at a relatively early age – even in their late twenties. Finding these people at a young age is crucial, otherwise they risk heart attacks and strokes in their late thirties or early forties.

‘I would like to use these tools to find people who have the same kind of fingerprints. There are people who have such high and such low cholesterol that it must be genetic. As we sit here we’re pretty healthy, but to find the functional variant that causes this disease is very difficult,’ said Prof. Kuivenhoven.

Currently, lipid-lowering drugs are prescribed to all patients with high risk of cardiovascular disease regardless of their age, gender or lifestyle. Prof. Kuivenhoven is advocating for individualised care.

7. The Implementation of Pharmacogenetics in Personalised Medicine in the US Presented by Prof. Dan Roden, senior vice president for Personalised Medicine at the Vanderbilt University Medical Centre, Nashville Tennessee, United States of America?

Prof. Roden spoke about the importance of pharmacogenetics, or the study of how genes affect a person’s response to drugs. He quoted a 2009 interview with Francis Collins, saying that pharmacogenetics will undoubtedly become a very compelling part of medical practice.



Prof. Roden then presented the Vanderbilt PREDICT project, which stands for the Pharmacogenomic Resource for Enhanced Decisions In Care and Treatment. This initiative selects populations of patients that are at high risk for receiving a drug with variable outcomes known to be associated with genetic variants.

These patients are then be genotyped pre-emptively on a platform that assays many pharmacogenomic variants. The genotypes are then stored and the informatics tools to provide point-of-care advice are developed, and the outcomes tracked.
‘If we had the genetic [information], we estimated we could have avoided between 300 and 400 serious medical events over a 5 year period,’ said Prof. Roden. ‘However, clinicians want to hear yes or no, and geneticists are working in shades of grey.’

The first step that the PREDICT project took was to identify patients that did not respond well to a particular drug. The first drug chosen was clopidogrel (tradenamed Plavix), and poor metabolisers of this drug have a higher risk of heart attack or other complications after a coronary stent. Whether or not a person is a poor metaboliser of clopidogrel can be determined by checking their CYP2C19 genotype. Genetically-determined decreased CYP2C19 activity results in decreased anti-platelet effect of clopidogrel, with risk of in-stent clotting, heart attack, stroke or death.

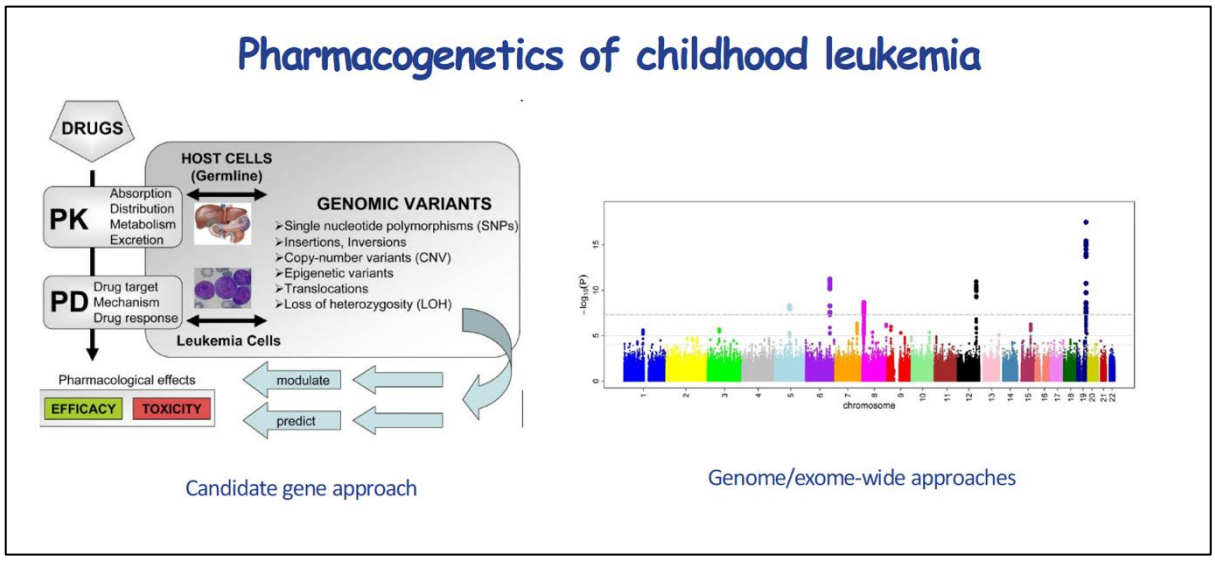
Following the tests, the patient data was aggregated on a website and the patient could log in and read their individual sensitivities to 5 specific commonly-used drugs – clopidigrel or plavix, a blood thinner, simvastatin or zocor, used to lower bad cholesterol, tacrolimus and thiopurines, both types of immunosuppressants, and warfarin, used to treat blood clots. Over 15,000 patients have been tested since the program started in 2010.

8. Pharmacogenetics in Paediatric Hemato-Oncology
Presented by Prof. Maja Krajinovic, professor of the departments of Paediatrics and Pharmacology at the University of Montreal, Canada

Prof. Krajinovic took leukaemia, the most common type of childhood cancer, as the main focus of her discussion. Since 1960 there has been a steady increase in 5-year survival rates of paediatric patients less than 15 years old, with 88% of all patients now surviving more than 5 years after diagnosis.

Of course, all treatments for leukaemia involve toxicities, and the therapies are extremely harsh on the body systems. Treatment protocol usually involves an induction period of 28 days, followed by central nervous system (CNS) treatment for 3 weeks, an intensification period where medication is administered in a 3-week cycle for 30 weeks, and these cycles will continue for 2 years.

Pictured below is a description of the pharmacogenetics of childhood leukaemia, and the genomic variants that may arise on both host cells and leukaemia cells.



Osteonecrosis is one of the major complications of all childhood treatment. Osteonecrosis occurs when blood flow to the bone is disturbed in some way, and the bone tissue begins to break down as a result.

'Given the complicated way of action of the corticosteroids, many groups are trying to understand which genes are involved in mediating the effects and which genes are induced by the corticosteroids,' said Prof. Krajinovic.

One of these genes' codes for pro-apoptotic protein is known as BIM. Prof Krajinovic's team analysed a number of polymorphisms in this gene and discovered that the polymorphisms can influence the chances of survival of the leukaemia patients as well as risk of osteonecrosis and were further involved as a key regulator of cell death.

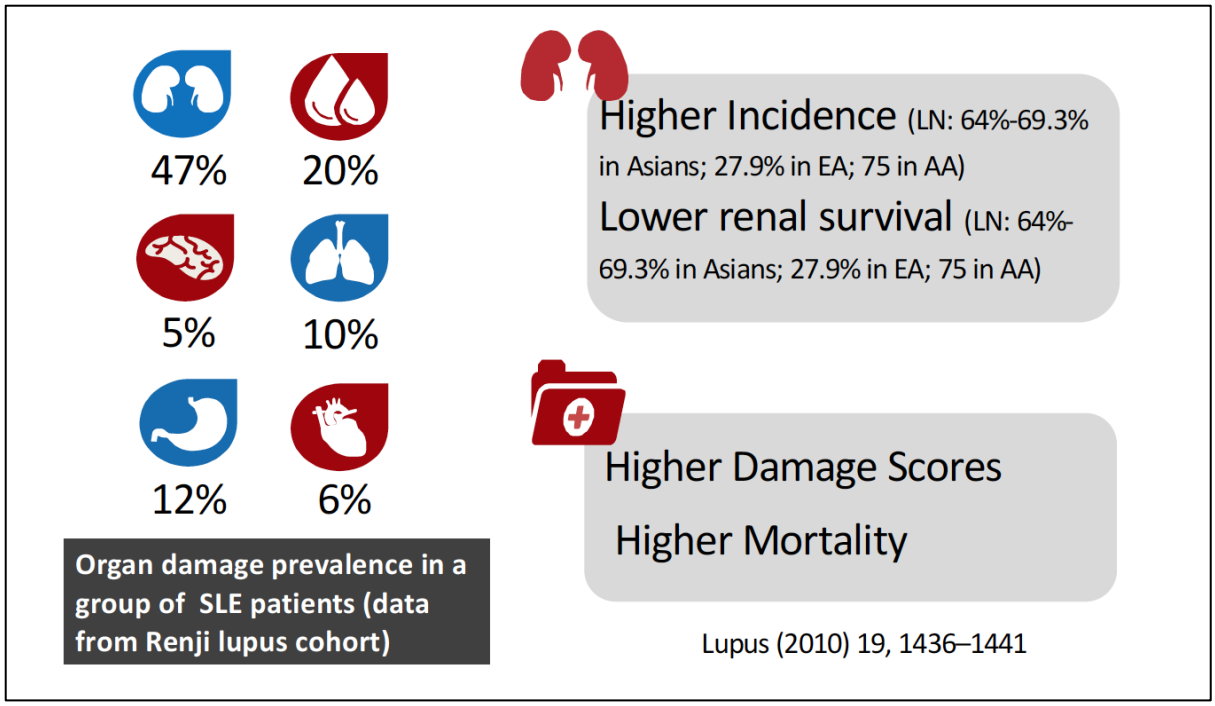
The team also analysed 4500 variances for several adverse potential consequences of asparaginase treatment, namely pancreatitis, thrombosis and allergic reactions. They found that the polymorphisms in MYBBP1A and interleukin 16 genes were associated with these complications.

She concluded that these genes have a pertinent function – the MYBBP1A gene plays a role in many cellular processes such as tumour suppression, cell cycle and mitosis, and as a co-repressor of the nuclear factor. The IL-16 gene encodes for a multifactorial cytokine and is involved in inflammatory and autoimmune diseases, cell control and cancer.

9. The Path to Precision Medicine: Lessons from Applying Personalised Immunology for Managing Autoimmune Diseases in China

Presented by Prof. Nan Shen of the Shanghai Institute of Rheumatology, Renji Hospital JiaoTong University School of Medicine, China

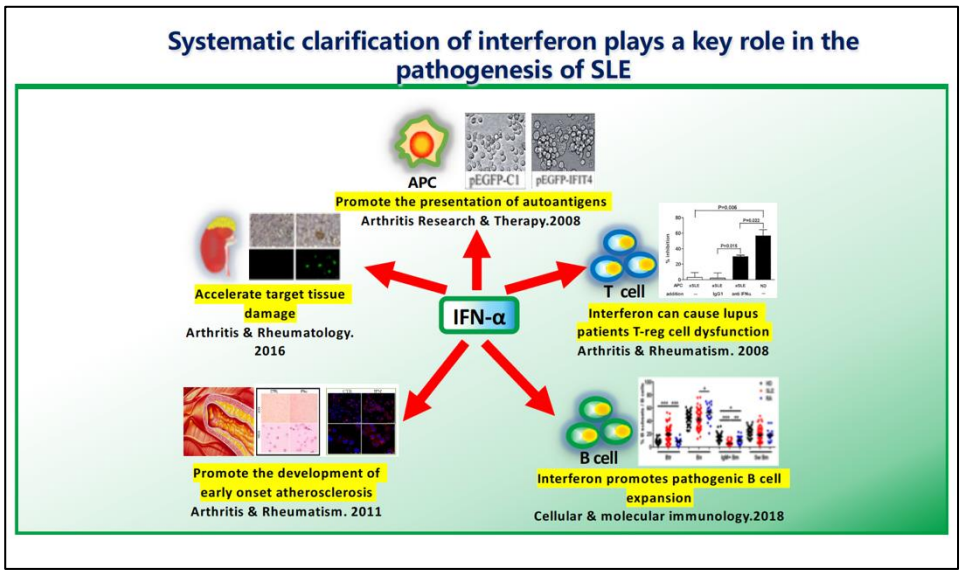
The prevalence of systemic lupus erythematosus (SLE) lupus in China is far higher than the prevalence of SLE in Europe – in China it is present in 50-100 cases out of every 100,000 citizens, whereas in Europe, it is only present in 27-40 cases. Chinese patients also suffer more organ damage from lupus than their European counterparts and have lower renal survival.



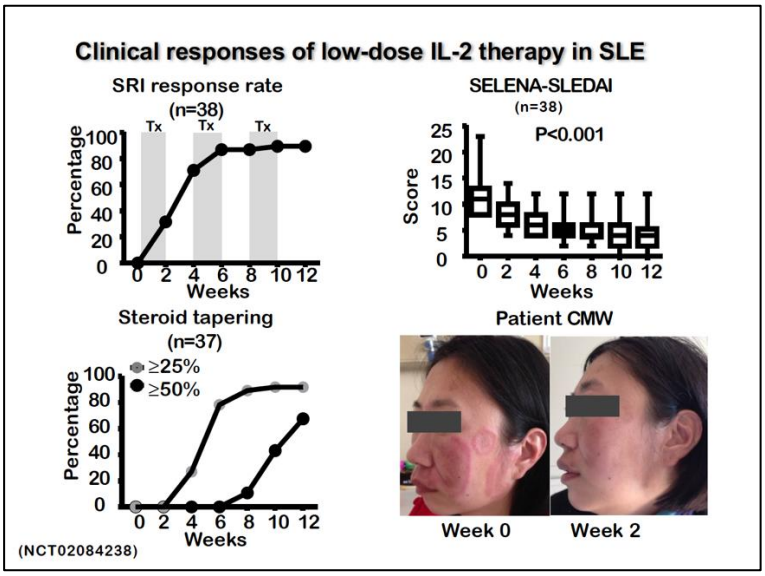
Prof. Shen's team saw that there was a lack of biomarkers for predicting organ damage and a lack of indicators for determining the activity of the disease despite the fact that there was high heterogeneity in the pathogenesis of SLE patients.

It is known that the interferon (IFN) "signature" in peripheral blood: major molecular phenotype for human lupus and the IFNIG expression signature in blood cells of SLE patients is highly reproducible from multiple microarray studies. Shen's team found that IFN scores and levels of LY6E expression were elevated in patients with lupus nephritis more notably in those with current renal flare. They identified a new SLE-susceptible gene NCF1 which determined the abnormal activation of the interferon pathway. The primary lupus risk factors are functional variations within IFN signalling molecules.

According to Prof. Shen, systematic clarification of interferon is vital for SLE's pathogenesis:



Immune phenotyping was carried out by Prof. Shen's team, and they saw that the frequency of transitional B cells and IL-6 producing transitional B cells were significantly reduced in SLE patients with effective treatment. The team then tried out low-dose IL-2 therapy, and found that in two weeks there was a significant improvement.



Prof. Shen's team also tried to find urine biomarkers to predict renal activity and prognosis. They found 12 valid proteins.

Precision Medicine – Implications for Patients

10. Pharmacogenetics of Adverse Drug Reactions

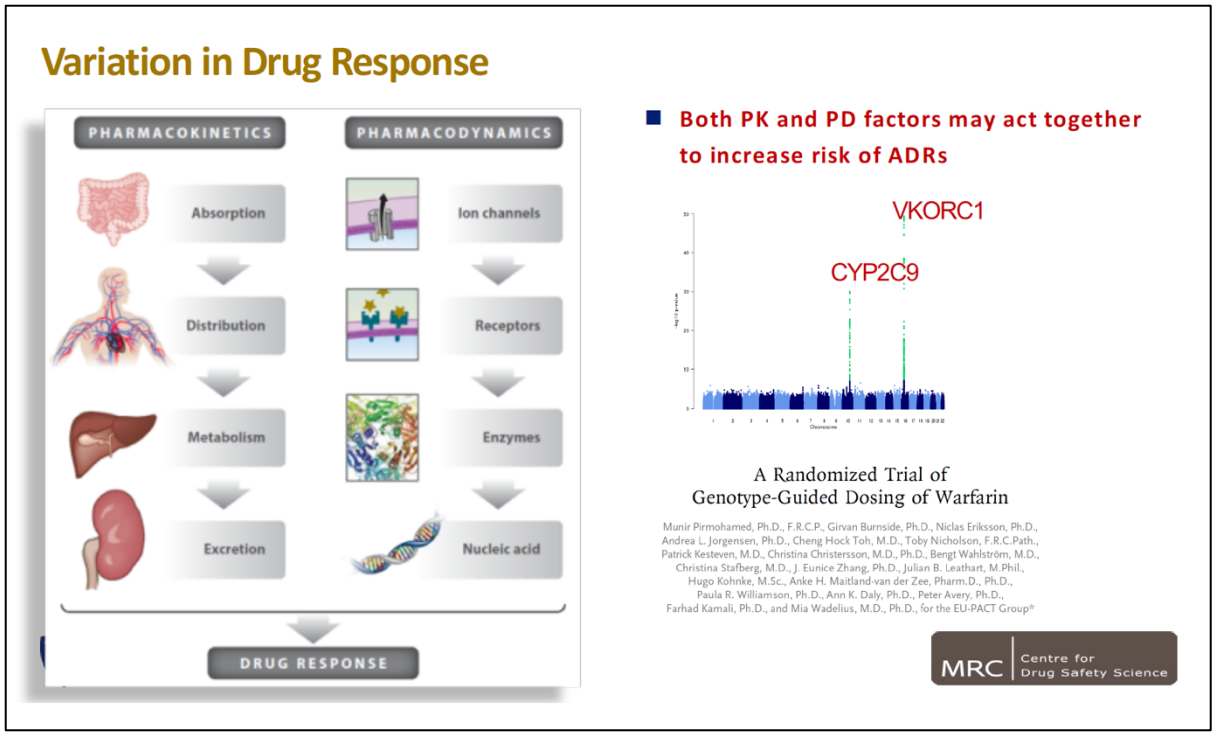
Presented by Prof. Munir Pirmohamed, the David Weatherhall Chair of Medicine at the University of Liverpool, United Kingdom

According to Prof. Pirmohamed, adverse reactions to drugs are responsible for 6.5% of all adult and 2.9% of all child admissions to hospitals in the UK. This costs the healthcare system around £1.6 billion per year.

"Clearly we want drugs that work on patients with specific diseases but unfortunately every drug has safety issues, and there's a risk-benefit that doctors need to look at," he said.

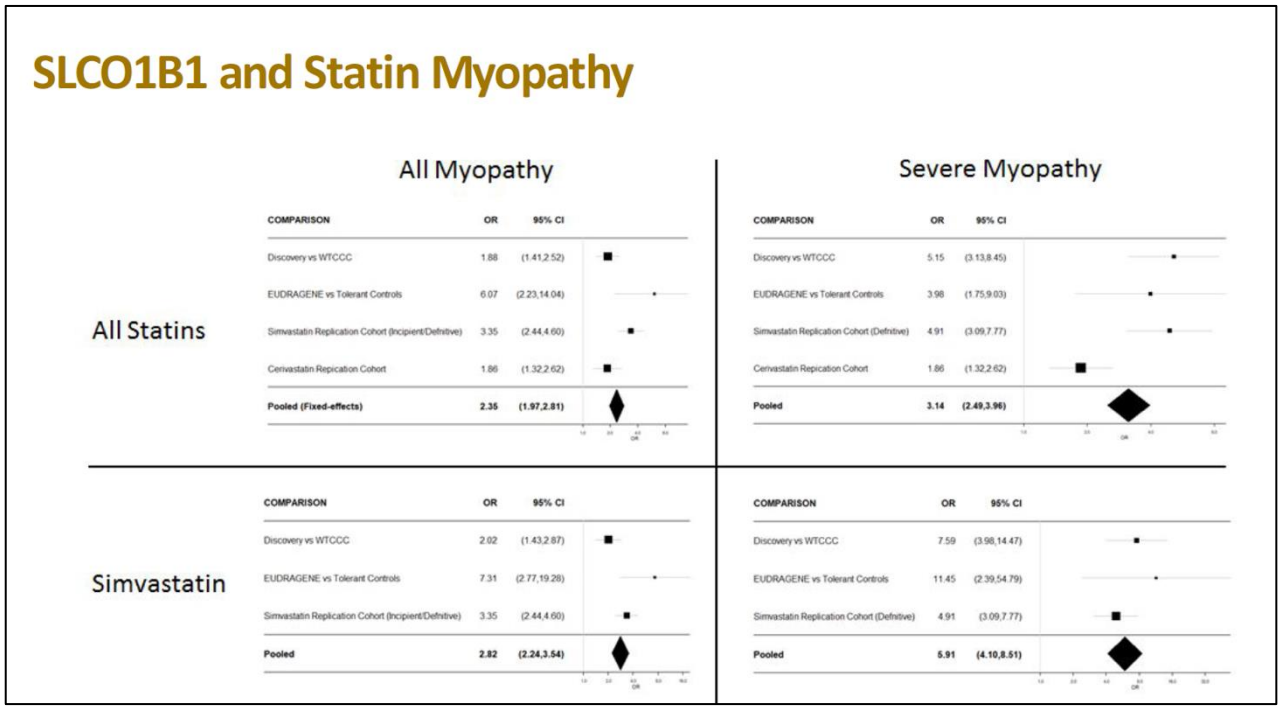
A patient generally suffers from one of two basic types of adverse drug reaction – Type A or Type B. The Type A reaction is predictable from the known primary or secondary pharmacology of the drug, and characteristically exhibits a clear dose-dependence relationship. On the other hand Type B reactions are not predictable from the basic pharmacological knowledge of the drug and there is often a complex dose-dependence relationship.

Pharmacokinetic and pharmacodynamic factors can determine whether a patient will have an adverse drug reaction or not. By acting together, they can further increase the risk of adverse drug reactions.

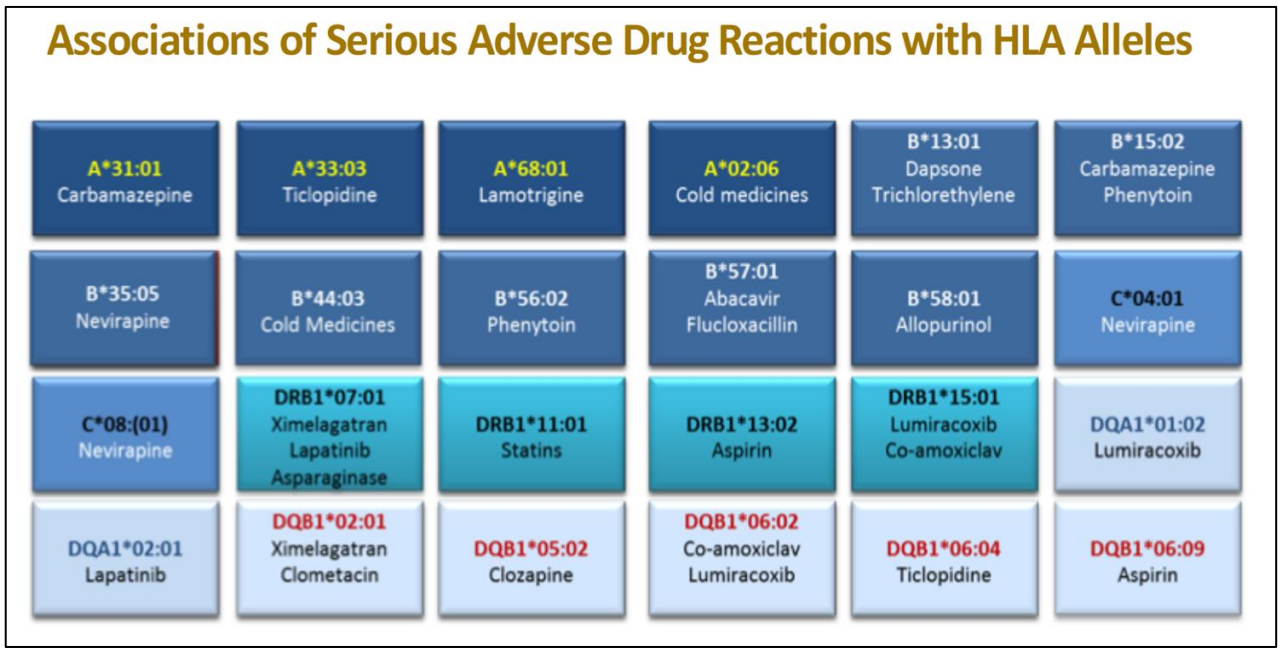


Prof. Pirmohamed said that a criticism of pharmacogenetics has been that although we know about these polymorphisms, very little has been translated into clinical practice. 'How can we do this in the future?' he asked.

Prof. Pirmohamed gave an example of the SLCO1B1 sequence and statins, the simvastatin in particular. The dosing table describes how statins should be prescribed with reference to the SLCO1B1 genotype.



A panel was developed by Prof. Pirmahamed and his team which aims to speed up testing for risk alleles.



11. Data to the People – MIDATA Personal Data Cooperatives
Presented by Prof. Ernst Hafen, Institute of Molecular Systems Biology, ETH Zurich, Switzerland

What if all your health data was stored in a bank, where only you had the key and only you could decide who gets to use it? Your information could still be used by scientists and health professionals, but you could restrict companies from accessing it, or vice versa, as you wished.

Google knows more about your health than your doctor

That's the premise that the MIDATA Personal Data Cooperative is based on – a bank of all your digital health data, but only you can grant access for it to be used.

"When a cooperative is owned by citizens, we find that what is generated is given back to society," said Prof. Hafen. You could allow your data to be used by research projects, government surveys, etc, and ensure that your data wasn't used by organisations or corporations whose goals you might not necessarily support.

Health data is already being collected by smartphones, according to Prof. Hahen. "Five years from now, this will be a medical device from which you can also make phone calls... Google knows more about your health than your doctor," he said.

Power can be given back to the individual through this cooperative bank, he said. It operates on a cloud-based secure platform where each record – whether it's your genome or the steps you take – are individually encrypted, and the only person who has the key is you.

Precision Medicine – Implications for Industry

12. Precision Medicine and Genomics – A Pharma Perspective
Presented by Dr Thorsten S. Gutjahr, Vice-President and Global Head of Companion Diagnostics, AstraZeneca.

According to Dr Gutjahr, more than 90% of their NME clinical pipeline follows a precision medicine approach. He presented two examples of drugs made by AstraZeneca and showed how personalised medicine helped in their clinical development.

The first example Osimertinib isa medicine developed by AstraZeneca to treat locally advanced or metastatic non-small-cell lung cancer. The clinical studies for the drug were hugely positive in phase 1 and phase 3. Osimeritinib is an irreversible inhibitor that is selective for epidermal growth factor receptor - tyrosine kinase inhibitors (EGFR-TKI)-sensitive mutations (Ex19 deletions and L858R) as well as for the T790M 'resistance' mutation.

At tumour progression after a 1st generation EGFR-TKI, scientists learned that there were different kinds of mutations and genetic aberrations happening that were contributing to this resistance. Often, a T790M mutation was involved.

If a cancer patient has the T790M mutation, and is treated with Osimertinib, the chance that the tumour shrinks is very high – according to the clinical study data. Overall, the development of this drug was very fast – it took less than three years from 'first time into man' to receiving US approval.

Olaparib was another example that was presented. It's a so-called 'PARP inhibitor' and approved for ovarian and breast cancer patients, but also in development for other cancer indications.

Osimertinib and olaparib are prime examples for precision medicines targeting patients that benefit most

What are PARP inhibitors? Single strand breaks occur in the DNA in our cells every day, and a polymerase called PARP repairs these breaks. If PARP is not working or blocked, e.g. through a PARP inhibitor, double strand breaks occur. However, our cells repair these kinds of breaks through a process called homologous recombination repair.

Unfortunately, some cells are deficient in the ability to carry out homologous recombination repair, they are so-called 'HRR deficient'. The most prominent cells with this deficiency are those that carry BRCA mutations in the BRCA1 or BRCA2 genes. In these cells, double-stranded breaks can no longer be repaired, and more mutations accumulate within the cells and the cells eventually die.

BRCA1 and 2 are well-known for being large and highly complex genes – Dr Gutjahr said, "The challenge was how we take such complicated genes with their many mutations and

develop a companion diagnostic for identifying the right patients that benefit most from olaparib"

Olaparib works by targeting tumour cells that are HRR deficient and killing them. AstraZeneca is currently running clinical studies that look at a variety of tumour indications that are HRR deficient. Clinical studies are ongoing in ovarian, breast, prostate and pancreatic cancers.

Precision Medicine – Implications for Policy

13. Personalised Healthcare: Policy and Practiced Progress

Presented by Denis Horgan, European Alliance for Personalised Medicine Executive Director, Brussels, Belgium

Denis Horgan is the Executive Director of the European Alliance for Personalised Medicine (EAPM), an organisation based in Brussels that lobbies the European Commission & Parliament to ensure that Europe's patients have early access to personalised healthcare and to boost public health research. The goal of EAPM is to facilitate patients' access to innovative medicine and optimise the use of existing regulatory tools. Two key areas for EAPM are big data and Health Technology Assessment (HTA).

Some important issues, Horgan said, are: how can we get innovation in the healthcare sector? How can we facilitate this at policy level? "The reality is that sometimes we hear about wonderful science but the challenge arises when we attempt to integrate it into the public healthcare system," he said.

30% of global scientific output is generated in Europe

There's a discrepancy between Europe's stunning scientific track record – 30% of global scientific output is generated in Europe, though Europeans make up only 7% of the world's population – and the amount of innovations and profit-making enterprises that are generated here. There is a large research-to-market gap, and although it is closing, progress is still slow compared to Europe's global competitors. An increase in research and innovation investment of 0.2% of GDP would result in an increase of 1.1% GDP in productivity growth.

By 2022, MEGA aims for there to be access to 1 million genomes in the EU

Horgan addressed Juncker's Ten Point Plan, which failed to list healthcare as a priority for the European Union. However a key outcome of the Lamy report, the advisory document on maximising the impact of the next Horizon Europe funding programme, was that a mission-focused approach should be adopted.

Horgan also discussed MEGA (Million Europeans Genome Alliance), whose vision is "to leverage the shared knowledge and resources from sequencing one million genomes catalogued other patient data to discover and develop new personalised therapies and diagnostics to benefit patients globally". By 2022, MEGA aims for there to be access to 1 million genomes in the EU.

The idea is to leverage and maximise the investments already made by Member States at national and EU level, particularly in sequencing, biobanking and data infrastructure.

Different countries have different national strategies, however many are now aligned with one approach. MEGA identified 6 core enablers across the countries' individual action plans: 1. A citizen/patient-centred approach; 2. Ethical principles and supportive legislation; 3. Novel partnership models for academic and commercial innovation; 4. Access to genome sequencing technology; 5. Capable information systems and 6. An educated and engaged healthcare workforce.

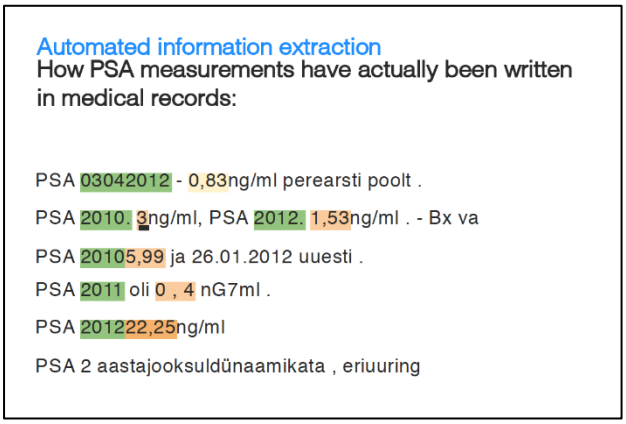
14. The Estonian Personalised Medicine Initiative

Presented by Prof. Jaak Vilo, Institute of Computer Science, University of Tartu, Estonia

In 2000 the Estonian biobank was established, with 52,000 original participants - an additional 100,000 were added in 2018. Currently, the bank holds health records of approximately 5% of the Estonian population, and by the end of 2018 that figure will be 15%. The types of data stored by the biobank include health records, diet, physical activity, DNA, plasma and cell samples. To date, 3,000 samples have been fully sequenced and almost all have been genotyped.

The Estonian population carries an e-card issued by the government authorities. On this card, health and social security information can be stored. The card has become a platform for healthcare billing and for e-prescriptions – 99% of Estonians now receive digital-only prescriptions. It can also be used to store medical health records, which is an extremely important source of data for the Estonian biobank.

The new system also allows for the cleaning up of data – below you can see an image of how prostate-specific antigen (PSA) measurements had been handwritten in medical records previously. The new system allows for streamlining and alignment of data. The system allows for health mining data of more than 1 million individuals. Genomics data can also be linked to the electronic health record (EHR) to provide researchers with a more complete picture.



According to Prof. Vilo, the biobank can provide patients with pharmacogenetic information, warning patients that they should stop using a particular drug or suffer adverse effects. Diabetes, for example, is predictive, and a high risk of diabetes combined with even a moderate level of overweight can be a really bad situation. 'Everyone should get this checked,' said Prof Vilo.

The system can also be used to determine risk of familial hypercholesterolemia, or FH. FH is a genetic disorder, caused by a defect on chromosome 19. The defect makes the body unable to remove low density lipoprotein (LDL, or bad) cholesterol from the blood. The resulting high levels of bad cholesterol in the blood make the patient more likely to suffer from stroke or heart attack at a younger age.

Prof. Vilo emphasised that local research is needed – genetic differences in local populations means that one study can't be taken and applied to all situations. But Estonia and Finland now provide subcontracting services for other countries, which can provide advice, he said.

15. Perspectives for Public Health Genomics within a Healthcare System Context
Presented by Dr. Marc Van den Bulcke, Department of Immunology, Sciensano, Belgium

Prof. Van den Bulcke presented Belgium as a case study of how to integrate genomics into a healthcare system context.

The Belgian initiative started, he said, when the government was approached by scientists asking for a budgetary increase for marker diagnostics because of the high prices associated with next generation sequencing. The government were starting to look at companion diagnostics and targeted therapy in cancer studies at the time. Feasibility studies were carried out and it was decided to integrate omics into the public healthcare system.

A proposal including a number of recommendations was put forward in March 2015. A pilot phase of the project will being in January 2019. A key feature will be structural reimbursement of both the drugs being tested and the costs of the tests themselves. Prof. Van den Bulcke outlined his so-called "roadbook" for implementing next-generation sequencing in clinical practice of oncology and hemato-oncology.

Roadbook for the implementation of next-generation sequencing in clinical practice in oncology and hemato-oncology	
ACTION 1	Establish a commission: Commission Personalized Medicine (ComPerMed)
ACTION 2	Development of guidelines for NGS use in (hemato)-oncology
ACTION 3	Development of criteria for NGS use in (hemato)-oncology
ACTION 4&5	Develop and organize a benchmarking trial and EQA for NGS use in (hemato)-oncology
ACTION 6	Implement NGS registration, storage and data management
ACTION 7	Provide NGS education and training
ACTION 8	Informed consent, legal and ethical implications of NGS use in (hemato)-oncology molecular diagnostics
ACTION 9	Pilot study 'NGS use in routine diagnostics'
ACTION 10	Build on hospital networks for NGS use in (hemato)-oncology

Belgium set up a Commission of Personalised Medicine which brought clinicians, scientists and technical consultants together to discuss the best way to proceed.

The first task was to develop a guideline on how to do Next Generation Sequencing in the Clinic, which was published in 2017. The next thing that the Commission had to do was decide how to classify all the markers. It was agreed that there should be three levels, called test levels.

He then expanded on the concept of genomic citizenship. Belgium wanted to talk to its citizens to ensure that they would have support from patients and also to ensure that patients would be willing to share the information that was generated through genome analysis.

In collaboration with the King Baudouin Foundation, Prof. Van den Bulcke carried out focus group studies to get informed public perspectives on the initiative. Over three weekends, a small cohort of 32 randomly chosen Belgian citizens came together and came up with conclusions that were presented to the Belgian health minister. There will also be a stakeholder report and a symposium at the end of 2019.

Prof. Van den Bulcke was overall impressed by the level of knowledge of the participants – most participants were familiar with the concept of personalised medicine.

Lastly, they surveyed general health in the population, and found that the genetic make-up of the population of bilingual Brussels is closer to that of Flanders than Wallonia.

16. Ethical imperatives for personalised medicine: A costly promise?

Presented by Prof. Joshua Hordern, Associate Professor of Christian Ethics at the University of Oxford, Oxford Healthcare Values Partnership, UK

Prof. Joshua Hordern laid out several ways in which personalised medicine costs the patients, the researchers and society as a whole. He warned that the cost to lives lived should not be forgotten while the scientific community and society are absorbed by the idea and promise of precision medicine.

In terms of patients, he remarked on the phenomenon of exclusion from certain trials leading to disappointment or pressure to participate and that there was a need for more qualitative research on the perception of risk and future. In relation to breast cancer care, he mentioned evidence of disintegration rather than personalisation, quoting *Day, S et al*: "staff and patients alike find themselves in pieces, scattered along the pathway and struggling to put the parts together." He explained that the patient's journey can be disrupted as compassionate companionship suffers in the face of rising complexity.

For researchers, he indicated ongoing research into the pressures researchers face to ensure that trials don't fail, and asked whether this burden of expectations is too heavy.

For governments, he said that the promise of precision medicine is that it seems to bypass intractable problems in societal health, and that it seems to be independent of patient behaviour and environmental outcomes. He drew on research which investigated whether the UK government's support of the 100K genome project was overly enthusiastic. He warned that attention and funding could be distracted from the "seemingly intractable" grind of behaviour change, patient responsibility and environmental improvements.

He cautioned that these costs may pose a threat to the idea of "genomic citizenship", a concept upon which genomic medicine seems to depend. He said that ethnographic, psycho-social and ethical reflection may reduce hype and improve the ethos and policies pertaining to personalised medicine.

Partners and organisers

The Federation of European Academies of Medicine (FEAM) is the European umbrella group of 19 national Academies representing thousands among the best biomedical scientists across Europe and disciplines with the mission to provide independent, evidence-based biomedical and health policy advice. The Swiss Academy of Medical Sciences (SAMS) was founded in 1943 and it currently comprises 253 elected members, numerous commissions and working groups. The academy is committed to high-quality medicine based on ethical principles. It supports early-career researchers and engages with academia and practice. With its expert and advisory activities, the SAMS also serves policymakers and the public.

Rue d'Egmont, 13
1000 Brussels | Belgium
+32 (0)2 793 02 50
E-mail: info@feam.eu
Twitter: @FedEuroAcadMed
www.feam.eu

Haus der Akademien
Laupenstrasse 7, CH-3001 Bern
+41 31 306 92 70
mail@samw.ch