Priorities for Research in Stratified and Personalised Medicine

Research Priority Workshop Report

Wednesday 24 July 2013

Manchester Conference Centre

Dr Natalie Carter
Research Liaison Manager at Arthritis Research UK
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Goals of the day and the view of Arthritis Research UK

Alan Silman
Medical Director, Arthritis Research UK

This meeting is intended as a forum to guide Arthritis Research UK Clinical Study Groups (CSGs), as they develop their research priorities for clinical studies targeted at disease sub-groups.

It is important to note that we are discussing stratified medicine rather than medicines - which in addition to pharmaceuticals covers other therapeutic areas such as devices, rehabilitation therapies etc. The terms ‘personalised’ and ‘stratified medicine’ tend to be used interchangeably. The former is best reserved for the individual disease and personal characteristics, whereas the latter should be restricted to the molecular or cellular defined subtypes that might influence treatment response.

There are three scenarios for new research in this area:

1. Testing of novel diagnostics to stratify a current therapy
2. Testing of novel therapeutics based on stratification by an existing diagnostic
3. Testing of the co-development of novel diagnostic and therapeutic

Research into biomarkers can help to avoid the side-effects of treatments, may produce economic gains or produce a more effective way to decide on a treatment for a given patient. Research may apply to single or multiple biomarkers addressing single or multiple treatments.

A central question in the stratified and personalised medicine agenda is whether patients understand the consequences of the results of stratified medicine research.

Opportunities and challenges for stratified and personalised medicine

Munir Pirmohamed
Head of Molecular and Clinical Pharmacology, University of Liverpool

Despite disease classification by patient phenotype, which can be augmented by histology, diseases are largely treated as being the same. Personalised medicine holds out the prospect of individualising treatment for each patient, although this may be a long way from the rheumatology clinic.

Molecular definition to allow disease stratification will be based on pharmacogenomics and other ‘omics’ approaches. We now have the capability to generate large volumes of data very cheaply. Thus the UK must build expertise and capacity in handling this kind of ‘big data’.

There is a heavy health and economic burden of adverse drug reactions in the UK - 8000 beds per day in NHS. Stratified medicine has the capacity to identify patients that will have adverse reactions. Abacavir (HIV drug) hypersensitivity has been associated with HLA-B*570. After 2006, this genotype was tested for in each HIV clinic in the UK and has resulted in adverse reactions dropping from 7% to virtually none. Similarly, people who developed statin myopathy were identified using the Clinical Practice Research Datalink (CPRD) with linked DNA samples. However, to utilise these samples for research required 132 R&D approvals across primary care in the UK, with the process taking over a year. This level of regulatory bureaucracy needs to be overcome.

Clinical trials to validate each biomarker/diagnostic may be neither necessary, nor affordable and it may be better and more cost effective to use newer ways of generating evidence.

There are many issues to consider with the stratified and personalised medicine agenda, and these are more wide-reaching than simple medical questions. These include:

- Legal, ethical and social issues
- Privacy and confidentiality of genetic information
Priorities for Research in Stratified and Personalised Medicine: Research Priority Workshop

- Changing physician behaviour
- Fairness of using this information
- Stigmatisation
- Health inequalities - will this be the preserve of the rich?

Different perspectives on stratified and personalised medicine

1. NIHR perspective

Rajesh Thakker
Chair, Efficacy and Mechanism evaluation program, NIHR/MRC, University of Oxford

The Efficacy and Mechanism Evaluation Programme (EME) is a collaborative project between the MRC and NIHR with the aim of ensuring that the right patient gets the right treatment at the right time. EME identifies key groups of patients with distinct phenotypes on the basis of disease mechanisms or response to treatments. The aim is to use this information to avoid the overuse of drugs, surgery and other therapies.

The EME programme supports excellent clinical science not only to ask the question ‘does it work?’ but whether it can work within the NHS. From over 100 expressions of interest, 6 research projects are now fully funded. One such grant, for £1m, was awarded to Queen Mary College, University of London for the use of synovial biopsy histology to stratify response to anti-TNF in Rheumatoid Arthritis (RA).

The EME criteria for success included:
- Science - potential to make significant breakthroughs in understanding and future discovery work
- Benefits to the patients and public
- High impact on both the individual and the NHS
- Deliverability
- Wealth - potential to reduce costs and enhance commerce

2. Industry perspective

Ruth March
VP and Head Personalised Healthcare & Biomarkers, Astra Zeneca

Astra Zeneca (AZ), and indeed every large pharmaceutical company is now active in this. During 2013 there have been five personalised health care drugs and nine companion diagnostics approved. This represents more than 75% of all oncology approvals for 2013, and stratified medicine is now becoming part of mainstream healthcare.

Stratified medicine is very attractive to pharmaceutical companies as it decreases the attrition rate and increases the chances of a drug making it to market. Currently more than 80% of the AZ healthcare pipeline is following this approach, covering all aspects from pre-clinical testing to marketing. This includes a GM-CSF drug for RA. Although much of the activity has been in oncology, the Kinsey report suggests that arthritis (immune-related disease) should be delivering personalised healthcare in approximately three years.

However there are significant challenges in stratified medicine. This type of development requires close working with mathematicians in order to develop robust clinical decision tools. Moreover, timelines for FDA/regulatory approval are a significant hurdle.
3. Patient perspective

Simon Denegri  
Chair, INVOLVE

There is a clear need for a cross stakeholder approach to promote public dialogue in the stratified medicine agenda but there is currently no strong evidence around public views on personalised medicine.

Generally people are very positive about their involvement in research. However, experience of engagement within the clinic is poor. This agenda may force clinicians to have a shared decision making process with their patients.

Key issues from patients were identified as:

- Basis of science - how long will it take, and why can this not happen tomorrow?
- Deep-seated concerns about inequity and being priced out of good healthcare.
- Availability of educated and trained clinicians, and also training for patients.
- Will this allow us to get closer to shared decision making?
- View of collectivism, how to respect diversity but still have a collective voice?

We need to focus our efforts into two areas: collecting a strong evidence base and fostering collaborations between stakeholders. The message for Arthritis Research UK is that the USER group is a good model to guide stakeholder input into research decision making. There is now a need to specifically focus on the patient priorities in personalised medicine. Furthermore, as the stratified medicine agenda evolves there will be an increased need for high quality information for patients. It is essential that the public are well informed and educated in this area and charities have a role to play in this agenda.

4. Clinical research perspective

Ann Morgan  
Professor of Molecular Rheumatology, University of Leeds

Stratified medicine is essentially based on grouping patients based on their likelihood of response to therapy, using diagnostic tests and techniques. The UK is well placed to lead in this area due to NHS data as well as academic/industrial potential. NIHR has formed Diagnostic Evaluation Cooperatives to ensure biomarker research is robust as well as clinically valid.

There are academic challenges in undertaking stratified medicine research in the field of RA:

- Pooling data from existing longitudinal observational studies is needed but they are variable with different end-points, data collection and samples taken. Clinical trials tend to use highly selected groups and may not represent real world data.
- Few biomarkers are at the stage of clinical validation.
- Biobanks are traditionally not funded alongside clinical trials.

INBANK, an Arthritis Research UK initiative, provides biobanking and infrastructure needed for collecting minimal core data sets that can then be incorporated in future clinical studies.

However, there are currently large numbers of competing research/biobanking initiatives. This kind of collaborative infrastructure based research is inadequately recognised by the REF, making this type of work less attractive. In combination with reduced funding and staffing, this creates a challenging environment.
Arthritis Research UK should have a role in two areas:

1. Using CSGs to co-ordinate collaborative UK clinical research, driving the national agenda and identifying opportunities across many funding bodies.
2. INBANK should have as a major aim delivering a stratified medicine agenda with the need to develop biobanks.

5. Health economics perspective

Katherine Payne
Professor of Health Economics, University of Manchester

The health economic challenge is to inform the people making decisions about how to allocate scarce resources for most benefit. Stratified medicine research is currently directed towards targeting of oncology medicines using a biomarker or genetic-based diagnostic to identify eligible patients, although programmes for cancer screening and indeed rheumatoid arthritis are under consideration.

One mechanism to provide evidence to decision-makers is utilising an economic evaluation framework for measuring the added value of stratification. Within this framework the input is the costs of treatment and the outputs are clinical measures such as quantified symptom relief, quality adjusted life years and life years gained. In principle this framework is a useful tool but is very difficult to generate based on real-world clinical data.

An attempt to generate an evaluation framework to assess the clinical effectiveness of genotyping women with breast cancer to guide the value of treatment with tamoxifen led to the conclusion that there was a poor (unfocussed) clinical evidence base, derived from 34 studies of 24 separate patient cohorts. This made meta-analysis of these studies impossible.

There is currently a strong focus on oncology and on stratified, rather than personalised medicine. There is also a paucity of robust economic data. Value-based pricing is on the horizon and collecting and collating the correct, robust economic data is necessary.

6. Clinical practice perspective

Stefan Siebert
Senior Lecturer in Rheumatology, University of Glasgow

Within the clinic there are a number of barriers to stratified medicine. Firstly, there is uncertainty about grouping patients, as many have multiple co-morbidities. Moreover, existing guidelines for treatment are based on unselected patients. The clinician also needs to appreciate that chronic conditions change over time and treatment needs to be refined as symptoms vary.

Stratified medicine has already been applied to oncology, and this is often highlighted as the exemplar for how stratified medicine could and should operate. The application of stratified medicine to rheumatology, however, may prove to be difficult for a number of reasons:

- Increased multifactorial influences on disease outcome
- Heterogeneous disease phenotypes
- Thus far individual genetic factors only have a modest contribution on treatment outcome
- Clinical outcomes, rheumatology is unlike cancer where survival is easily measurable. ‘Softer’ outcomes are needed in rheumatoid arthritis and related disorders
- Tissue diagnosis is not part of standard care
In order to overcome these barriers in rheumatology, new biomarkers must be developed designed to work well in a clinical setting. These should be easily accessible and non-invasive, timely at point of clinical contact, quicker than trial and error and also cost effective. Ideally, therapy would be combined with a companion diagnostic, but this has an increased cost. The rheumatology team would also need clear, objective early outcome measures to prove that an intervention is having a clinical impact.

7. Technology Strategy Board perspective

Alasdair Gaw
Lead Technologist, Technology Strategy Board (TSB)

TSB is a UK Quango that specifically funds companies to develop new products and services [https://www.innovateuk.org/](https://www.innovateuk.org/). This organisation was set up in 2007 to identify the UK capability to innovate and fund new products and services from concept to delivery, within industry.

The stratified medicine agenda is covered by TSB and defined as the ‘use of diagnostic tests for therapy selection.’ Already in the UK in vitro diagnostic industry has a turnover of £1.1 billion. TSB aims to provide a platform to accelerate development and uptake of the stratified medicine agenda by investing £200 million over five years. Both the NIHR and MHRA advise TSB and its recently produced ‘Roadmap’ for Stratified Medicine includes:

- Incentivising adoption
- Increasing awareness
- Enhancing patient recruitment
- Improving data-collection, management and use
- Ensuring regulation and standards are fit for purpose
- Addressing the IP issue
- Development of appropriate biobanks and biomarker testing

Within **Round 1**, TSB invested £9.5 million into projects including the development of point-of-need diagnostics for hepatitis and identification of inflammatory biomarkers within RA and COPD. There were also four projects focussed around tumour profiling.

Within **Round 2**, TSB invested £6.5 million combined with £1 million from DH. This funded four projects assessing heath economics.

**Round 3** comprised of £7.5 million investment from TSB to stimulate clinical imaging technologies that can be used for stratification. From 46 applications, 28 reached the second stage.

**Round 4** will involve the investment of £4.5 million from TSB to enabling tissue sampling and handling combined with analysis and storage.

There are a number of routes for academia to interact with TSB. The Knowledge Transfer Partnership scheme is to support post-docs, and other academic experts, to work within industry. Academics may also enter the stratified medicine space through collaborative work with industry.
Current status of approaches to research in stratification

1. Genetics

Bill Newman
Senior Clinical Lecturer Genetic Medicine, University of Manchester

Dr Newman focussed his talk not on the use of genetics in targeting therapy but in unravelling disease causes in subsets that might be used as a spring board for developing new treatments, illustrating the case for stratified medicine using clinical examples.

Meningioma is a common central nervous system tumour, more common in women than men (3:1 ratio). Exome sequencing of rare, dominant families, who develop spinal meningioma disease, showed that a mutation in SMARCE1 was involved. This allows new treatments to be developed based on the disease mechanism.

The progressive disease, Leri’s pleonosteosis, causes restricted joint motion as well as fused vertebrae and scleroderma. Familial genetic testing identified chromosomal changes resulting in overexpression of BMP-13 and Syndecan-2 in tissue, leading to patients presenting with large volumes of extra extracellular matrix. This allows clinicians to choose a treatment option based on this phenotype.

2. Metabolomics

Roy Goodacre
Professor of Biological Chemistry, University of Manchester

Metabolomics has the potential to be a useful tool in terms of biomarker discovery and testing for stratified medicine, although research is at an early stage. There are many platforms available to analyse metabolite profiles. The USERMET project (funded by MRC and BBSRC) is designed to profile metabolites in human serum both in health and disease. Over 2000 of 3500 samples from healthy individuals have been analysed, thus far.

The metabolomics of a super organism such as man are complex and the data that emerge include: human, microbial, nutritional metabolites and xenometabolites. To properly generate profiles with an acceptable signal to noise ratio, there is a need to control for diet, sample time, BMI and personal characteristics, such as gender. Consequently there are only around 50 published studies focused on metabolomics in arthritis and many of these are not excellent quality.

3. Patient factors

Nadine Foster
Professor of Musculoskeletal Health in Primary Care, Keele University

Patient stratification has proved to be a useful tool for managing patients with low back pain (LBP). For this group with non-specific low back pain their first contact with a clinician is generally a GP. This is generally first managed with advice and analgesia which can be stepped up to physiotherapy exercises and manual therapy. If the patient is still in pain they would then be referred to a specialist clinic.

The challenge for GPs is to spot which patients will or will not do well, so that patients can be quickly matched with the correct treatment. The Keele group’s ten year programme of subgrouping patients with LBP was used as the basis for developing prognostic risk factors to identify patients with a high risk of chronicity. The resulting ‘STarT Back’ screening tool was developed in 2004-5.

This tool went through independent validation and an independent pilot study to test acceptability and feasibility. The tool identified independent prognostic factors that can predict a poor functional outcome.
The factors included were:

- referred leg pain
- co-morbid pain elsewhere in the body
- fear avoidance
- anxiety
- catastrophising
- depression
- overall impact

The screening tool, an online resource with a low number of questions, places patients into low, medium or high risk groupings.

1. Low-treatment opinion: advice, reassurance and pain relief with one consult with GP
2. Medium-treatment opinion: evidence-based course of physiotherapy
3. High-treatment opinion: psychologically-informed physiotherapy

The RCT involved 2,793 patients, randomised between stratified and control group. Patients were monitored at four and 12 months and significantly different outcomes were shown between the two groups. In addition, the STarT back tool was £34 cheaper on a per patient basis. This work was published in *The Lancet* in 2011.

The follow-up work (IMPacT) aims to establish if the tool can be implemented within health care systems and assess the effects, including costs. The results of this study are impressive: with usual care 40% of high risk patients were referred to the specialist clinic, whereas with STarT back 76% of the high risk patients were referred. Time off from employment was halved, and disability was significantly reduced.

**Priorities for stratified / personal medicine**

Each of Arthritis Research UK’s eight Clinical Studies Groups had been consulting with their ‘community’ on priorities for Stratified medicine research and the group leads reported to the meeting on their priorities.

1. **Inflammatory arthritis in adults**

   *John Isaacs*

   *Chair, Adult Inflammatory Arthritis, Newcastle University*

   There is an on-going debate as to whether RA is a joint disease, an immune disease or even a vascular disease. Many view RA as a complex and variable autoimmune disease.

   There are some generic design points for stratified medicine projects that are cross-cutting regardless of the disease type:

   - There is a clear need to distinguish prognostic markers from markers that can be used for treatment stratification.
   - There is a need to better measure clinical outcomes. Some are objective, e.g. CRP, others are subjective e.g. tender joint count. Health economic arguments rely heavily on quality of life measures, which are also subjective.
   - When to measure outcome is not clear? At least 6 months post-treatment is required as some secondary non-responders are evident at this stage.
   - Biobanking - it is essential to have the right infrastructure in place and to exploit it for downstream mechanistic information.
   - Potential stratifiers may be clinical phenotypes rather than specific molecular/laboratory tests.
Some prognostic indicators e.g. illness perception may not influence treatment response.
There is a need for cross-disciplinary teams with all necessary expertise including users, industry, biostatisticians and clinicians.

2. Osteoarthritis and related disorders

Phil Conaghan
Chair, Osteoarthritis and Crystal Diseases, Leeds

Osteoarthritis represents a particular challenge for stratified medicine. There are very few treatment response indicators, at any joint site, that have been validated. Moreover, there are no markers to guide treatment at present. There is extensive on-going research into imaging and other biomarkers. However, the current situation is to include pain (above a certain level) as both a diagnostic tool and an indicator of clinical improvements.

3. Auto-immune rheumatic disorders

David Jayne
Chair, Autoimmune Rheumatic Disorders, Cambridge University

Patients with identical phenotypes with this group of disorders can have very different treatment responses. Understanding the disease mechanisms can open up possibilities for new therapies e.g. metabolic data can suggest anti-interferon therapy in Sjögren’s syndrome.

There is a desperate need for international registers for studying rare diseases, and for these to be properly communicated to all stakeholders. Common repositories in rare diseases are very powerful but we need organisations (funders and institutions) to allow repositories, registries and biobanks to work collaboratively.

4. Spondyloarthropathies

Neil McHugh
Chair, Spondyloarthropathies, Royal National Hospital for Rheumatic Diseases

Spondyloarthropathies (SpA) can be grouped into axial and peripheral spondyloarthropathy groups. Therapies may be specific to the two groups, or generic. Specific targets are treatments that inhibit osteolysis and those that stimulate new bone formation. The issue is that both of these processes may well be occurring in the same patient.

The spondyloarthropathy CSG identified three key research questions that required a stratified medicine approach:

1. Which patients with SpA are most likely to benefit from targeting IL-17 mediated pathways?
2. How may the benefits of exercise and self-management/coping be best evaluated using a stratified approach?
3. Dose-optimisation of anti-TNF

5. Metabolic bone disease

David Reid
Chair, Metabolic Bone Disease, University of Aberdeen

Prof. Reid stated that stratification is already in use in clinical practice for metabolic bone disease although this was more in selection of patients for treatment rather than stratifying disease subgroups e.g. FRAX tool for fractures. There is a question over whether there is actually a need for any further
stratification. In osteoporosis, 90% of people who take bisphosphonates benefit from the treatment. There may be the potential to use patient stratification for newer, more expensive therapies for osteoporosis e.g. Denosumab (£366 pa).

Paget’s disease is more common and is currently treated when pain is present. The PRISM study used a bone marker to stratify patients for treatment with bisphosphonates - this was found to be unhelpful. A newer RCT, called ZiPP (zoledronate in prevention of Paget’s), aims to stratify patients based on SQSTM1 genotype.

6. Regional and widespread musculoskeletal pain

David Walsh
Professor of Rheumatology, University of Nottingham

The key is whether patients can be stratified based on pain severity rather than on the mechanism of their pain. Classification of pain could be used to treat patients based on their prognosis. However, this approach may cause some problems as only those most likely to benefit are offered treatment. Other patients may feel that they have not been offered the best possible care.

The Pain CSG has identified three key priority areas for stratified medicine approach:

1. Fibromyalgia
2. Older people
3. Back pain

The application of stratified medicine to fibromyalgia would be difficult, due to a lack of appropriate biomarkers. The notion of stratified care was appealing but very few specific research questions emerged. This CSG suggested observational studies would be needed, to validate biomarkers as a first step in the process.

7. Musculoskeletal disorders in childhood

Michael Beresford
Chair of Pediatric Rheumatology, Liverpool University

There seems to be value in stratifying patients and then using existing therapies. There is current work to investigate the mechanism of disease and use this to inform treatments. For example: http://www.ncbi.nlm.nih.gov/pubmed/23620557

Serum MRP8/14 can be used in juvenile idiopathic arthritis (JIA) to predict disease relapse following withdrawal of methotrexate treatment.

The current hypothesis is that stratification based on disease biology or genetic and serum/cellular biomarkers can predict outcome (response, tolerability and adverse drug reactions) in children with inflammatory arthritis. In order to test this hypothesis, there is a need for routine collection of biological samples prior to start or switch of medications for all patients, in combination with good patient reported outcomes. There are already some good, established national cohorts: JIA (3000+) and SLE (400+). New networks are also being set up including childhood vasculitis and scleroderma.

- Data must be collected over the lifetime of disease, and treatments need to prevent long term disability and mortality.
- Sample collection needs to be acceptable and compatible.
8. Orthopaedic surgical interventions

Damian Griffin
Chair, Orthopaedic Surgery, Warwick University

There is need for a good evidence base, rather than using clinical instinct to choose surgical options. Stratification should be the basis of the choice whether to have an operation, and then be used to suggest a recommended procedure. Last year there were 80,000 hip replacement and 80,000 knee replacements. With these large numbers of patients it should be possible to collect and analyse data from which to give evidence based advice on treatment choice.

However, there are many different outcomes that should be used in assessing approaches to patient stratification with joint replacement. These include:

- Infection
- Dislocation
- Wear (surgical technique and implant design)
- Unexplained pain - due to both biological processes and patient factors. (This is the most difficult).

Stratification could have been useful in identifying patients that were suitable for metal on metal joint replacement surgery. Some patients had a severe reaction to metal debris, but this debris was inert for most. This treatment has now been withdrawn, even though it was effective in 80% of recipients.

Patient factors may be the most important indicators of whether a patient will be satisfied with joint replacement; these include pain severity, expectations and personality. Around 20% of patients are either not better, or not much better, following total knee replacement. This is not due to severe complications. It seems that predictors of this 20% could be identified either using imaging techniques or during the clinical examination. However, molecular diagnostics would not currently help to identify these people.

Panel discussion

The way forward for Arthritis Research UK

Debbie Cook
Director of National Ankylosing Spondylitis Society

- Much of today’s discussion had focussed on drug therapy.
- NAS surveyed 1000 members on our research agenda - most important questions were how to manage flares and fatigue and self-management.
- Patients want to see better diagnostic tools in order to stop people being ‘blocked’ by their GP for access to secondary care.
- Relevant patient organisations need to be collaborative to educate both patients and clinicians.

John Isaacs
Chair, Adult Inflammatory Arthritis, Newcastle University

- Optimistic about the value of a stratified medicine approach.
- Need to be careful about the comparison with oncology. Cancer is a very different set of diseases where histology is routine.
• Many rheumatological studies are much more heterogeneous and it is currently difficult to identify patient factors that influence outcome (in contrast to the conclusions about outcome from joint replacement surgery).
• Research must be initiated in a well-defined area, with clear measures of each parameter and to reduce confounders. This is the aim of the MATURA study.

David Isenberg
Professor of Rheumatology, University College London

Prof. Isenberg identified three key observations:

1. Incredible money is spent on identifying and monitoring patients to identify those who develop adverse reactions; it would be excellent to identify these patients early and swap therapy.
2. Collaboration between companies, clinicians and academics is necessary in order to advance stratified medicine.
3. A priority is the need to avoid steroids by stratification of patients and choose the correct biological therapy to use as soon as diagnosis is given.

Kalliope Panoutsopoulou
Sanger

• We are moving into an era when we can sequence everyone’s genome quickly and cheaply.
• Lowering costs will empower more studies on biomarkers.
• We need extensive work on phenotyping osteoarthritis to enable us to properly classify and stratify this heterogeneous disease.
• We need to find the right balance between having very large and powerful studies and stratifying patients into smaller groups.
• We need to engage with the public to allay fears about data.

Munir Pirmohamed
Head of Molecular and Clinical Pharmacology, University of Liverpool

• RA is the best exemplar within the field of rheumatology to try stratified medicine.
• Patient phenotyping needs to be embedded in every RCT to enable retrospective stratification of patients.
• We can use various biomarkers to stratify patients: imaging, DNA sequencing, etc. These are complementary rather than competitive.

Caroline Savage
Vice President and Head, Discovery Medicine, GlaxoSmithKline

• There is a sense of optimism - industry, clinicians, academics and funders are all speaking the same language.
• The bed-rock of medicine is to understand how to treat disease at early stages, before severe tissue damage. We need to use patient stratification to enable this early identification.
• Molecular and genomic information will impact on choices of treatment.

Allan Wailoo
Professor of Health Economics, University of Sheffield

• Health economics is already being embedded into many studies.
• There is an existing set of drug treatments that could be better targeted for both health and economic benefits.
• There are questions about how pharmaceutical companies will respond to developing new therapies for smaller groups of patients?
General discussion

There was little time for general discussion but amongst the comments made were:

- The regulators cannot necessarily agree on how to stratify the use of new drugs e.g. FDA approved Belimumab whereas NICE did not.
- Who is going to pay the price of extensive phenotyping of patients? It is extremely difficult to get funders to pay for this type of research, and the NHS will not fund these studies.
- There is a need for a robust NHS data infrastructure, linking primary, secondary and tertiary care in order to collect the necessary data to inform stratified medicine data.
- Cancer Research UK help to ensure that patients are registered into RCTs and that all data is correctly collected, maybe Arthritis Research UK should play a similar role.
- There is a need to lower the barriers to participation, and properly support infrastructure and research nurses.

There has been extensive discussion in the Pain CSGs about how Arthritis Research UK will not fund either prospective or epidemiology studies of treatment. If this is set to change it will need to be properly communicated with researchers. In the cancer field, there is much expertise in ‘big data’ especially in USA. Within the UK our strength is much more in the field of early phase studies. Perhaps we should allow other experts to do the detailed analysis.

Summary of the day

Alan Silman
Medical Director, Arthritis Research UK

A report from this strategy workshop will be written and published on the Arthritis Research UK website. The CSG leads will be responsible for feeding this information back to their respective CSGs.

Arthritis Research UK is very interested in funding research to predict why certain patients respond to treatment when others do not. This could be based in either clinical or molecular techniques.

It is clear from today’s discussions that different disease areas are at very different stages within the process of being able to research and implement stratified medicine. This workshop has given us a valuable opportunity to understand the landscape and survey the problems involved. We are very grateful to all the attendees for giving their time and expertise, especially those who are experts from outside the Arthritis Research UK family.
### Appendix 1: Programme

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<th>Event</th>
<th>Speaker/Position</th>
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<tbody>
<tr>
<td>9:00</td>
<td>Introduction and goals of the day</td>
<td>Alan Silman, Medical Director, Arthritis Research UK</td>
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<tr>
<td>9:15</td>
<td>Opportunities and challenges for stratified and personalised medicine</td>
<td>Munir Pirmohamed, Head of Molecular and Clinical Pharmacology, University of Liverpool</td>
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<td>9:45</td>
<td>Different perspectives on stratified and personalised medicine</td>
<td><strong>NIHR</strong>  Rajesh Thakker, Chair, Efficacy and Mechanism evaluation program, NIHR/MRC, University of Oxford</td>
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<td><strong>Industry</strong> Ruth March, VP and Head Personalised Healthcare &amp; Biomarkers, Astra Zeneca</td>
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<td><strong>Patient</strong> Simon Denegri, Chair INVOLVE</td>
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<td>10:40</td>
<td>BREAK</td>
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<td>10:55</td>
<td>Clinical research</td>
<td>Ann Morgan, Professor of Molecular Rheumatology, University of Leeds</td>
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<td>Health economics</td>
<td>Katherine Payne, Professor of Health Economics, University of Manchester</td>
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<td>Clinical practice</td>
<td>Stefan Siebert, Senior Lecturer in Rheumatology, University of Glasgow</td>
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<td>Technology Strategy Board</td>
<td>Alasdair Gaw, Lead Technologist Technology Strategy Board</td>
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<td>12:00</td>
<td>Current status of approaches to research in stratification</td>
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<td>Genetics</td>
<td>Bill Newman, Senior Clinical Lecturer Genetic Medicine, University of Manchester</td>
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<td>Metabolomics</td>
<td>Roy Goodacre, Professor of Biological Chemistry, University of Manchester</td>
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<td></td>
<td>Patient factors</td>
<td>Nadine Foster, Professor of Musculoskeletal Health in Primary Care, Keele University</td>
</tr>
<tr>
<td>13:00</td>
<td>LUNCH</td>
<td></td>
</tr>
<tr>
<td>13:45</td>
<td>Priorities for stratified / personalised medicine</td>
<td>John Isaacs, Chair, Adult Inflammatory Arthritis, Newcastle University</td>
</tr>
</tbody>
</table>

Each presentation will be followed by discussion.
### Priorities for Research in Stratified and Personalised Medicine: Research Priority Workshop 2013

<table>
<thead>
<tr>
<th>Priority Area</th>
<th>Chair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis and related disorders</td>
<td>Phil Conaghan, Chair, Osteoarthritis and Crystal Diseases, Leeds University</td>
</tr>
<tr>
<td>Auto-immune rheumatic disorders</td>
<td>David Jayne, Chair, Autoimmune Rheumatic Disorders, Cambridge University</td>
</tr>
<tr>
<td>Spondyloarthropathies</td>
<td>Neil McHugh, Chair, Spondyloarthropathies, Royal National Hospital for Rheumatic Diseases</td>
</tr>
<tr>
<td>Metabolic bone disease</td>
<td>David Reid, Chair, Metabolic Bone Disease, University of Aberdeen</td>
</tr>
<tr>
<td>Back pain and related disorders</td>
<td>David Walsh, Professor of Rheumatology, University of Nottingham</td>
</tr>
<tr>
<td>Musculoskeletal disorders in childhood</td>
<td>Michael Beresford, Chair, Paediatric Rheumatology, Liverpool University</td>
</tr>
<tr>
<td>Orthopaedic surgical interventions</td>
<td>Damian Griffin, Chair, Orthopaedic Surgery, Warwick University</td>
</tr>
</tbody>
</table>

15:05 **BREAK**

15:20 **Panel discussion**

The way forward for Arthritis Research UK

- **Debbie Cook** Director, National Ankylosing Spondylitis Society
- **John Isaacs** Chair, Adult Inflammatory Arthritis, Newcastle University
- **David Isenberg** Professor of Rheumatology, University College London
- **Kalliope Panoutsopoulou** Joint First Author, Sanger
- **Munir Pirmohamed** Head of Molecular and Clinical Pharmacology, University of Liverpool
- **Caroline Savage** Vice President and Head, Discovery Medicine, GlaxoSmithKline
- **Allan Wailoo** Professor of Health Economics, University of Sheffield

16:15 **Summary of the day**

16:30 **DEPART**
## Appendix 2: Attendees

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Specialism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Jenny Barrett</td>
<td>University of Leeds</td>
<td>Professor of Statistical Genetics</td>
</tr>
<tr>
<td>Professor David Beard</td>
<td>University of Oxford</td>
<td>Professor of Musculoskeletal Sciences</td>
</tr>
<tr>
<td>Professor Michael Beresford</td>
<td>Liverpool University</td>
<td>Chair Paediatric Rheumatology CSG</td>
</tr>
<tr>
<td>Dr Laura Boothman</td>
<td>Arthritis Research UK</td>
<td>Policy Manager</td>
</tr>
<tr>
<td>Dr Maya Buch</td>
<td>University of Leeds</td>
<td>Senior Lecturer/Honorary Consultant Rheumatologist</td>
</tr>
<tr>
<td>Dr Natalie Carter</td>
<td>Arthritis Research UK</td>
<td>Scientific Liaison Manager</td>
</tr>
<tr>
<td>Dr Hector Chinoy</td>
<td>University of Manchester</td>
<td>Senior Lecturer, Rheumatology</td>
</tr>
<tr>
<td>Professor Philip Conaghan</td>
<td>Leeds University</td>
<td>Professor of Musculoskeletal Medicine</td>
</tr>
<tr>
<td>Ms Debbie Cook</td>
<td>National Ankylosing Spondylitis Society</td>
<td>Director</td>
</tr>
<tr>
<td>Mr Simon Denegri</td>
<td>INVOLVE</td>
<td>Chair</td>
</tr>
<tr>
<td>Dr Will Dixon</td>
<td>University of Manchester</td>
<td>Honorary Consultant Rheumatologist</td>
</tr>
<tr>
<td>Ms Tracy Elliot</td>
<td>Arthritis Research UK</td>
<td>Research Programme Manager: Clinical Studies</td>
</tr>
<tr>
<td>Professor Nadine Foster</td>
<td>Keele University</td>
<td>Professor of Musculoskeletal Health in Primary Care</td>
</tr>
<tr>
<td>Dr Alasdair Gaw</td>
<td>Technology Strategy Board</td>
<td>Lead Technologist</td>
</tr>
<tr>
<td>Mr Siôn Glyn-Jones</td>
<td>University of Oxford</td>
<td>Senior Lecturer</td>
</tr>
<tr>
<td>Professor Roy Goodacre</td>
<td>University of Manchester</td>
<td>Professor of Biological Chemistry</td>
</tr>
<tr>
<td>Professor Damian Griffin</td>
<td>Warwick University</td>
<td>Chair Orthopaedic CSG</td>
</tr>
<tr>
<td>Professor Lorraine Harper</td>
<td>Birmingham University</td>
<td>Professor of Nephrology</td>
</tr>
<tr>
<td>Dr Nick Harvey</td>
<td>University of Southampton</td>
<td>Senior Lecturer and Honorary Consultant Rheumatologist</td>
</tr>
<tr>
<td>Dr Philip Helliwell</td>
<td>University of Leeds</td>
<td>Senior Lecturer in Rheumatology</td>
</tr>
<tr>
<td>Professor Ariane Herrick</td>
<td>University of Manchester</td>
<td>Professor of Rheumatology</td>
</tr>
<tr>
<td>Dr Pauline Ho</td>
<td>Manchester Royal Infirmary</td>
<td>Consultant Rheumatologist</td>
</tr>
<tr>
<td>Mrs Liz Holloway</td>
<td>Arthritis Research UK</td>
<td>Executive PA</td>
</tr>
<tr>
<td>Miss Margaret Hughes</td>
<td>Wrightington, Wigan &amp; Leigh NHS Foundation Trust Hospital</td>
<td>Lay representative CSG spondyloarthropathies</td>
</tr>
<tr>
<td>Dr Kimme Hyrich</td>
<td>University of Manchester</td>
<td>Reader in Rheumatic Disease Epidemiology</td>
</tr>
<tr>
<td>Professor John Isaacs</td>
<td>Newcastle University</td>
<td>Chair The Adult inflammatory arthritis CSG</td>
</tr>
<tr>
<td>Professor David Isenberg</td>
<td>University College London</td>
<td>Professor of Rheumatology</td>
</tr>
<tr>
<td>Dr Kassim Javaid</td>
<td>University of Oxford</td>
<td>Lecturer in Metabolic Bone Disease</td>
</tr>
<tr>
<td>Dr David Jayne</td>
<td>Cambridge University</td>
<td>NHS Consultant Physician</td>
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<tr>
<td>Dr Gareth Jones</td>
<td>University of Aberdeen</td>
<td>Senior Lecturer in Epidemiology</td>
</tr>
<tr>
<td>Name</td>
<td>Institution</td>
<td>Specialism</td>
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<tr>
<td>Dr Andrew Keat</td>
<td>Northwick Park Hospital</td>
<td>Consultant Rheumatologist</td>
</tr>
<tr>
<td>Ms Ruth March</td>
<td>Astra Zeneca</td>
<td>VP and Head Personalised Healthcare &amp; Biomarkers</td>
</tr>
<tr>
<td>Dr Jane Martindale</td>
<td>Lancaster University</td>
<td>Clinical Specialist Physiotherapist in Rheumatology</td>
</tr>
<tr>
<td>Professor Neil McHugh</td>
<td>Royal National Hospital for Rheumatic Diseases</td>
<td>Consultant Rheumatologist</td>
</tr>
<tr>
<td>Dr Rodger McMillan</td>
<td>RMM Healthcare Consulting</td>
<td>R&amp;D consultant</td>
</tr>
<tr>
<td>Professor Ann Morgan</td>
<td>University of Leeds</td>
<td>Professor of Molecular Rheumatology</td>
</tr>
<tr>
<td>Professor Mary Morgan</td>
<td>London School of Economics</td>
<td>Professor of History and Philosophy of Economics</td>
</tr>
<tr>
<td>Dr Bill Newman</td>
<td>University of Manchester</td>
<td>Senior Clinical Lecturer Genetic Medicine</td>
</tr>
<tr>
<td>Dr Wan-Fai Ng</td>
<td>Newcastle University</td>
<td>Clinical Senior Lecturer/Honorary Consultant in Rheumatology</td>
</tr>
<tr>
<td>Dr Kalliope Panoutsopoulou</td>
<td>Sanger</td>
<td>Joint first author</td>
</tr>
<tr>
<td>Professor Katherine Payne</td>
<td>University of Manchester</td>
<td>Professor of Health Economics</td>
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<tr>
<td>Professor Munir Pirmohamed</td>
<td>University of Liverpool</td>
<td>Head of Department of Molecular and Clinical Pharmacology</td>
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<tr>
<td>Professor David Reid</td>
<td>University of Aberdeen</td>
<td>Head of the School of Medicine &amp; Dentistry</td>
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<tr>
<td>Mr Matthew Rowbotham</td>
<td>Arthritis Research UK</td>
<td>Project Fellow</td>
</tr>
<tr>
<td>Dr Sarah Rudkin</td>
<td>Arthritis Research UK</td>
<td>Research Programme Manager: Clinical Initiatives</td>
</tr>
<tr>
<td>Professor Graham Russell</td>
<td>University of Oxford</td>
<td>Emeritus Professor of Musculoskeletal Pharmacology</td>
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<tr>
<td>Professor Caroline Savage</td>
<td>GlaxoSmithKline</td>
<td>Vice President and Head, Discovery Medicine</td>
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<td>Dr Stefan Siebert</td>
<td>University of Glasgow</td>
<td>Senior Lecturer in Rheumatology</td>
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<td>Professor Alan Silman</td>
<td>Arthritis Research UK</td>
<td>Medical Director</td>
</tr>
<tr>
<td>Mr Andrew Sprowson</td>
<td>Warwick University</td>
<td>Associate Professor of Trauma and Orthopaedic Surgery</td>
</tr>
<tr>
<td>Professor Rajesh Thakker</td>
<td>University of Oxford</td>
<td>May Professor of Medicine</td>
</tr>
<tr>
<td>Professor Wendy Thompson</td>
<td>University of Manchester</td>
<td>Professor of Genetic Epidemiology</td>
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<tr>
<td>Professor Allan Wailoo</td>
<td>University of Sheffield</td>
<td>Professor of Health Economics</td>
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<tr>
<td>Professor David Walsh</td>
<td>Arthritis Research UK Pain Centre</td>
<td>Director</td>
</tr>
<tr>
<td>Professor Lucy Wedderburn</td>
<td>Arthritis Research UK Centre for Adolescent Rheumatology at UCL</td>
<td>Director</td>
</tr>
<tr>
<td>Professor Gerry Wilson</td>
<td>University of Sheffield</td>
<td>Professor of Rheumatology</td>
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