Working Towards Implementation: A UK Perspective

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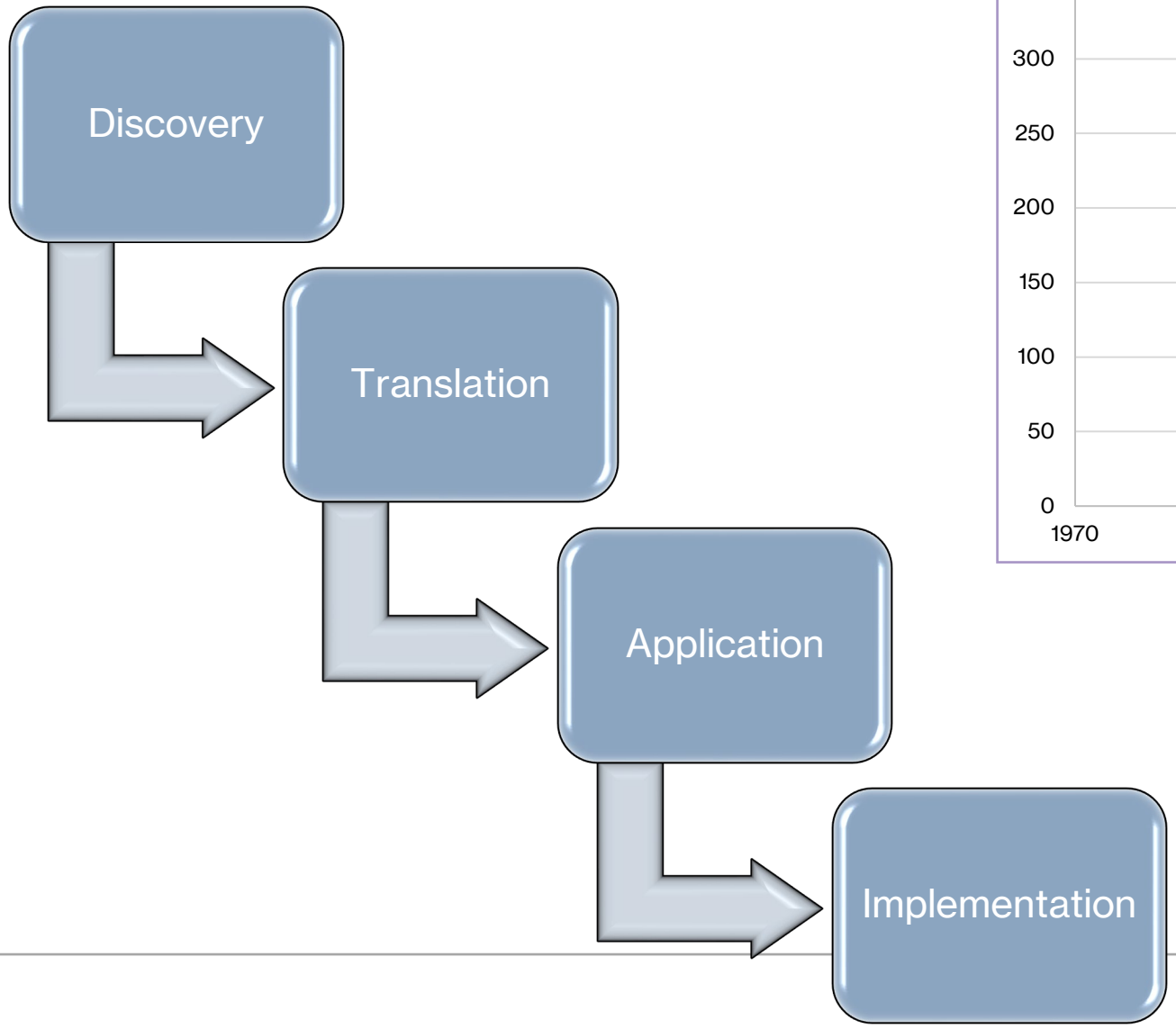
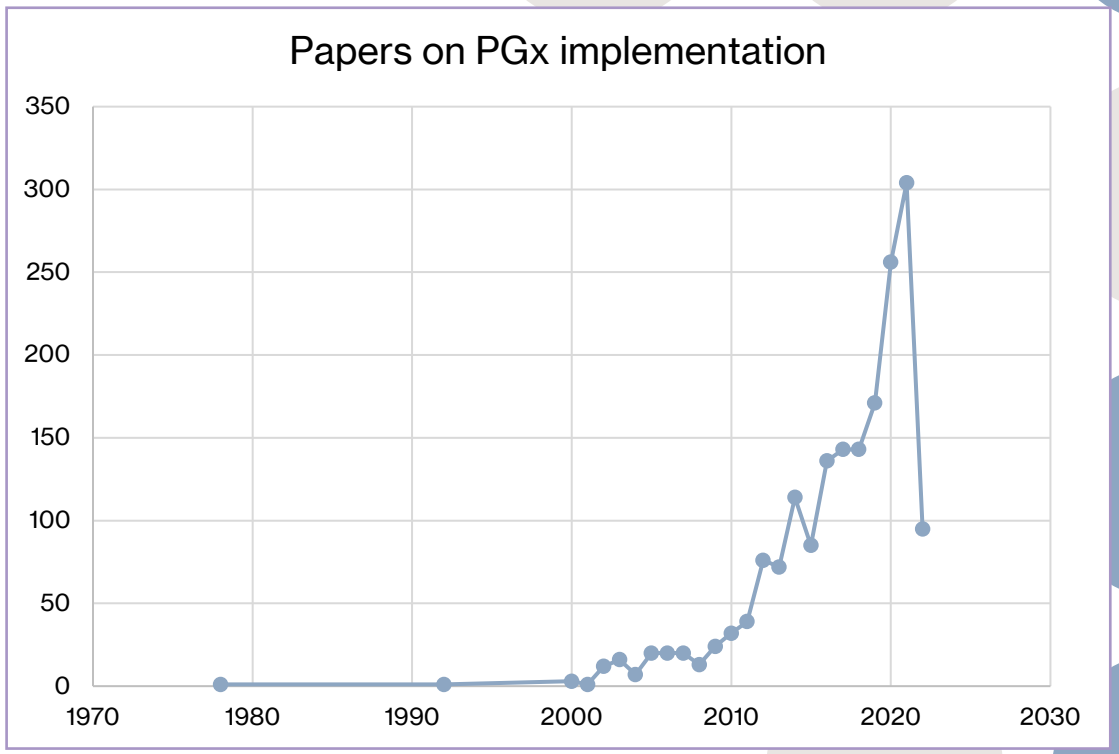
BRITISH PHARMACOLOGICAL SOCIETY

Research Spectrum





Abacavir Hypersensitivity

Association between presence of *HLA-B*5701, HLA-DR7*, and *HLA-DQ3* and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir

S Mallal, D Nolan, C Witt, G Masel, A M Martin, C Moore, D Sayer, A Castley, C Mamotte, D Maxwell, I James, F T Christiansen

Lancet 2002; **359:** 727–32

HLA-B*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D., Jean-Michel Molina, M.D., Cassy Workman, M.B., B.S., Janez Tomažič, M.D., Eva Jägel-Guedes, M.D., Sorin Rugina, M.D., Oleg Kozyrev, M.D., Juan Flores Cid, M.D., Phillip Hay, M.B., B.S., David Nolan, M.B., B.S., Sara Hughes, M.Sc., Arlene Hughes, Ph.D., Susanna Ryan, Ph.D., Nicholas Fitch, Ph.D., Daren Thorborn, Ph.D., and Alastair Benbow, M.B., B.S., for the PREDICT-1 Study Team*

N Engl J Med 2008;358:568-79.

Cost-effectiveness analysis of HLA *B*5701* genotyping in preventing abacavir hypersensitivity

Dyfrig A. Hughes[a], F. Javier Vilar[b], Charlotte C. Ward[a], Ana Alfirevic[a], B. Kevin Park[a] and Munir Pirmohamed[a]

Pharmacogenetics 2004, 14:335–342

- Pre-prescription genotyping is a cost-effective strategy
- Implemented in the UK from 2006 (before PREDICT-1)
- Incidence has decreased from 5% to <1%

Pharmacogenomics in the UK National Health Service: opportunities and challenges

doi: 10.2217/pgs-2020-0091

Richard M Turner[1], William G Newman[2], Elvira Bramon[3], Christine J McNamee[1], Wai Lup Wong[4], Siraj Misbah[5], Sue Hill[6], Mark Caulfield[7] & Munir Pirmohamed*,[1]

Table 1. Opportunities and challenges for implementing pharmacogenomics for a whole healthcare system.

Specific issues	Challenges	Mitigation
Type of genetic testing	Choice can vary from single gene, panels to whole exome/genome, each of which has its own advantages and disadvantages	Phased approach which can progress from single gene/variants, to panel based to whole-genome sequencing as technologies improve and costs decrease
Gene–drug pair associations to be included	No standardized list and variable numbers in different parts of the world	Include associations with the best evidence, and may have to use a phased strategy starting with a smaller number and increasing slowly.
Capacity for testing	On a country wide scale there may be concerns that the system may be overwhelmed	Limit the gene–drug pair associations included and have strict eligibility criteria for testing
Turnaround time for testing	If turnaround time is poor, the test will not be clinically useful and uptake may be low	Determine optimal turnaround time based on the drug, disease indication, and clinician input
Clinical effectiveness of pharmacogenetic testing	Evidence for the effectiveness of individual gene–drug pair associations may vary, and evidence for panel or sequencing approaches may be absent	Model the clinical effectiveness of panel-based testing using literature data. Implement real-world assessment of effectiveness using electronic health record data
Cost effectiveness of pharmacogenetic testing	Cost–effectiveness available for individual drugs but may be absent for panel approaches	Model the cost–effectiveness of panel-based testing using literature data. Implement real-world assessment of effectiveness using electronic health record data
Interpretation of pharmacogenomic test results	Knowledge about pharmacogenomics in healthcare professionals is poor	Inclusion of pharmacogenomic education in curricula and in clinical professional development courses for all professions
Lack of public awareness of pharmacogenomics	Poor awareness may lead to unrealistic expectations and/or poor uptake	Increase public education including clear information leaflets and materials. Online trusted resources also important
Decision support systems to help in interpretation and prescribing	Intelligent decision support systems are lacking	Start off with basic decision support and build up capabilities over time

Implementing Pharmacogenomic Testing in the NHS

- Cost effectiveness
- Operational implementation
- Eligibility criteria and volume of reporting
- Decision support tools
- Validation and reporting

Dihydropyrimidine Dehydrogenase (DPD) Genetic Testing

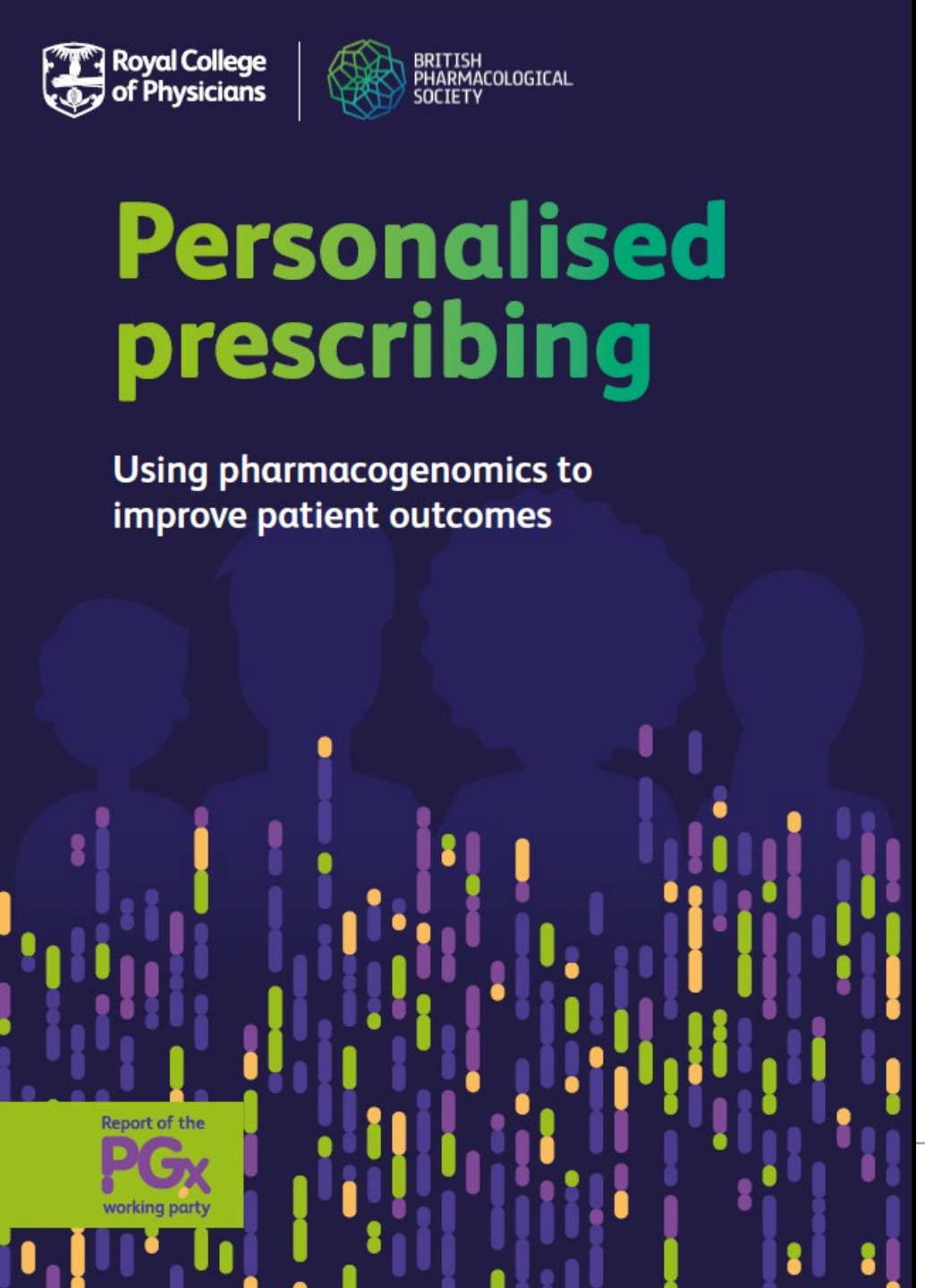
- DPD – an enzyme that detoxifies 5-fluorouracil, a chemotherapeutic drug used in about 15% of cancers
- Deficiency of DPD can cause bone marrow suppression and death
- Genetic testing introduced into NHS in 2020
- Also evaluated as a pilot in the 100K genomes project beforehand
- Wide take up (40000 tests per annum) – further review on-going to improve the clinical pathway

Mail Online

Revealed: How hundreds are being killed by chemo meant to save them (it's down to a little known side effect which can be avoided with a simple £60 blood test)

- Some genetic disorders mean patients can't process chemo drug capecitabine
- Dihydropyrimidine dehydrogenase (DPD) means the liver can't process the drug
- The deficiency is shared by five to eight per cent of the population

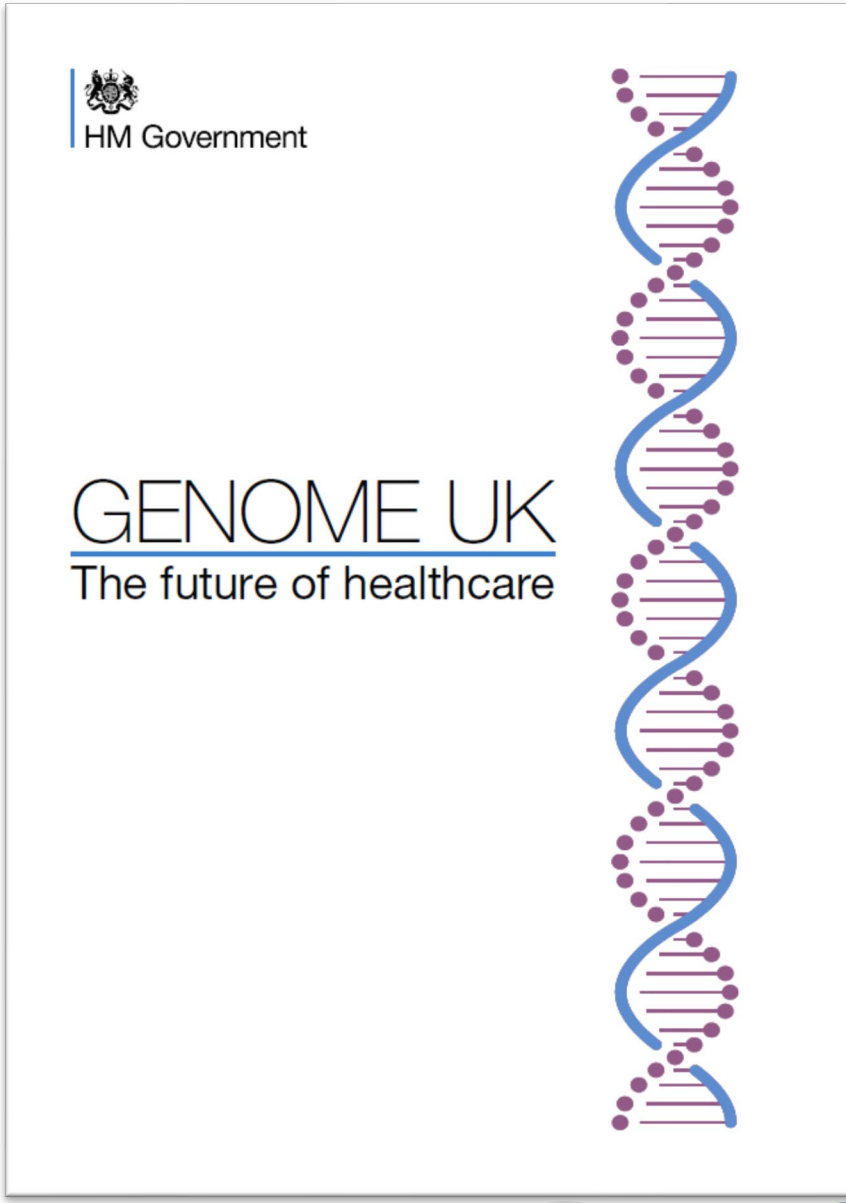
By DAVID ROSE
PUBLISHED: 22:01, 6 October 2018 | **UPDATED:** 22:02, 6 October 2018



Report published by Royal College of Physicians and the British Pharmacological Society

Implementation of Pharmacogenomics in the NHS

- Many drug-gene pairs have been identified which may potentially impact patient outcomes
- However, only a select few pharmacogenomic tests available in the NHS
- Guidelines have been produced by international groups
- Some sentinel sites in the US already implementing
- The NHS could be the first healthcare system to implement pharmacogenomics



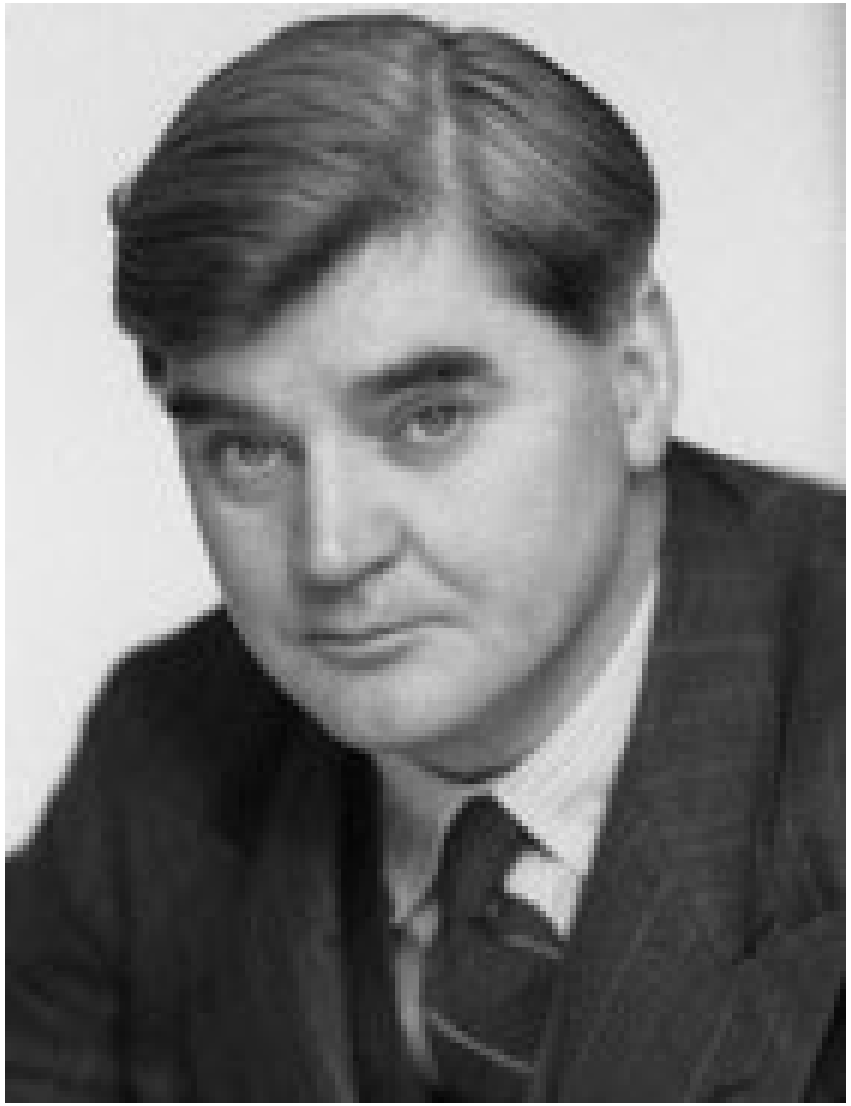
Working Party

Name	Representing
Professor Sir Munir Pirmohamed (co-chair)	British Pharmacological Society (BPS)
Professor Donal O'Donoghue* (co-chair)	Royal College of Physicians (RCP)
Dr Richard Turner (co-secretary)	BPS
Dr Emma Magavern (co-secretary)	BPS
Sophie Joseph (working party manager)	BPS
Deborah Roebuck	RCP Patient and Carer Network
Dr Paul Ross	Oncology
Professor Bernard Keavney	Cardiology
Professor Claire Shovlin	Respiratory medicine
Dr Joyce Popoola	Renal medicine
Dr Shuaib Nasser	Allergy and immunology
Dr Meriel McEntagart	Clinical genetics
Sonali Sanghvi	NHS England
Dr Anneke Seller	Health Education England
Dr Michelle Bishop	Health Education England
Professor Sir Mark Caulfield	Genomics England
Ravi Sharma	Royal Pharmaceutical Society
Dr Imran Rafi	Royal College of General Practitioners
Dr Jude Hayward	Royal College of General Practitioners

*Prof Donal O'Donoghue was involved in the early stages of the working party and report development. Following his death in January 2021, Dr Peter Belfield took over as interim RCP registrar until May 2021 when Dr Cathryn Edwards was appointed.

Deep Dives

Name	Representing
Dr Mario Juruena	Royal College of Psychiatrists
Dr Dan Hawcutt	Royal College of Paediatrics and Child Health
Professor Jaideep Pandit	Royal College of Anaesthetists
Dr Tariq Ahmad	Gastroenterology
Prof Guru Aithal	Hepatology
Dr Sanjay Sisodiya	Neurology
Professor Ewan Pearson	Endocrinology and diabetes
Professor Saye Khoo	Infectious diseases
Dr Sebastian Francis	Haematology
Dr Luigi Venetucci and Professor Bernard Keavney	Cardiology
Dr Joyce Popoola	Renal medicine
Dr Shuaib Nasser	Allergy and immunology
Dr Meriel McEntagart	Clinical genetics
Dr Paul Ross	Oncology
Professor Claire Shovlin	Respiratory medicine
Ravi Sharma	Royal Pharmaceutical Society and primary care
Dr Imran Rafi	Royal College of GPs and primary care
Dr Jude Hayward	Royal College of GPs and primary care
Dr Anneke Seller and Dr Michelle Bishop	Genomics Education Programme
Sonali Sanghvi	NHS England
Deborah Roebuck	Patients



The UK NHS

Founded on 5 July 1948

Underlying principle is to provide care at the point of need from cradle to grave

> “Illness is neither an indulgence for which people have to pay, nor an offence for which they should be penalised, but a misfortune the cost of which should be shared by the community.”

Evolution of the NHS

- With devolution, we have NHS bodies in the 4 nations
- Primary care is served by 2 electronic health record systems (EMIS and SystmOne)
- Secondary care is more diverse – many different EHRs, lack of interoperability etc

Four Nation Approach

Recommendations

- Clinical implementation of pharmacogenomics should occur in both primary and secondary care settings, as well as in specialised centres
- Mainstreaming pharmacogenomic services in the NHS throughout the UK should be commissioned and funded through the NHS National Genomic Test Directory, rather than locally driven
- Pharmacogenomic services will need to be agile and able to work at pace
- The implementation of pharmacogenomics should be accompanied by a comprehensive education and training package
- Support for clinicians should be provided as pharmacogenomic testing is rolled out
- Pharmacogenomic services should be subject to continuous and iterative evaluation
- Funding for pharmacogenomics research should be made available
- Pharmacogenomics implementation should be accompanied by clear lines of communication

Multi-Disciplinary Working

- Directed towards medical and non-medical prescribers
- Majority of drug prescribing occurs in primary care, while newer drugs are often first used in secondary care
- Clinical Pharmacologists and clinical pharmacists working with other specialties will be important in implementation
- Decision support systems are going to be important
- Complex cases may require multi-disciplinary team approaches

Consent

- Provide national standardised recommendations for consenting to tests specifically for pharmacogenomics.
- It is expected that most prescribers will be competent to routinely request consent to pharmacogenomic testing
- A pharmacogenomic test should be viewed as equivalent to renal or liver function testing to guide prescribing decisions
- Appropriate consent procedures required for whole genome sequencing conducted for other reasons, but it is important that pharmacogenomic information is not lost

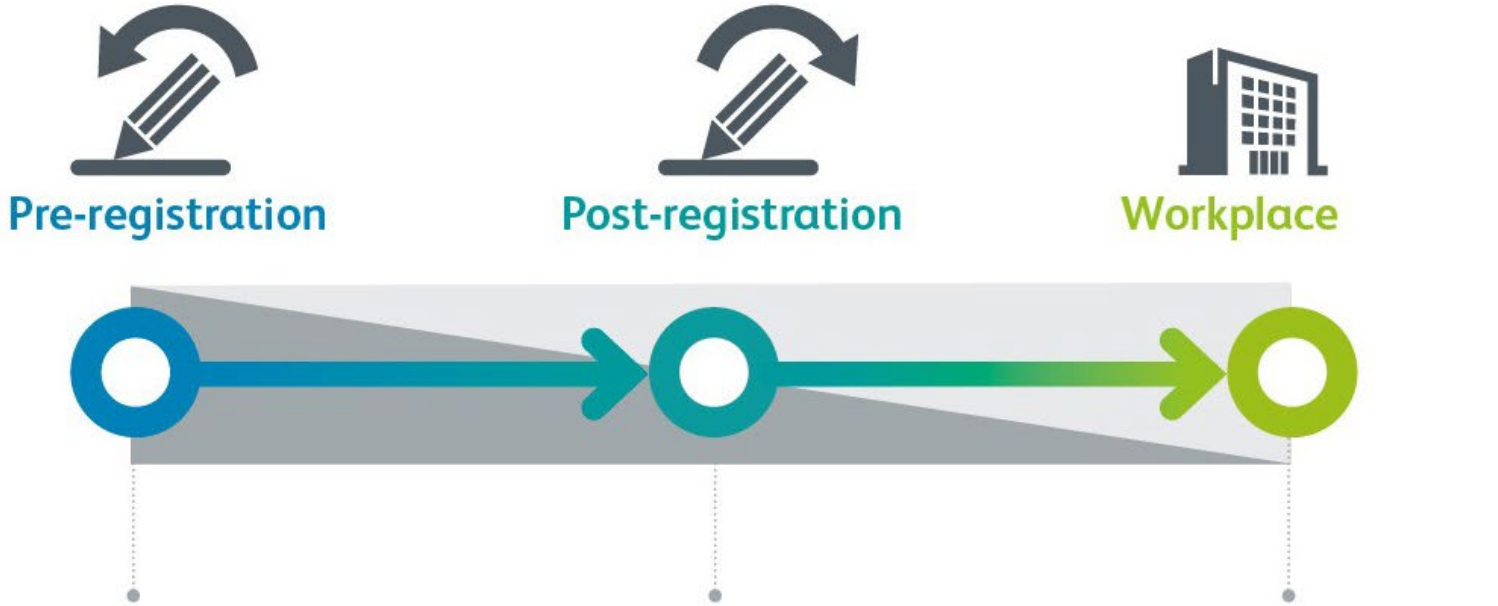
Genotyping

- Test a panel of pharmacogenes when pharmacogenomic information is the primary indication for testing. This approach provides results relevant for the immediate indication and pre-empts future prescribing.
- Extract pharmacogenomic information from sequence
- Ensure the test turnaround time is congruent with the chosen patient pathways
- Utilise point-of-care (POC) testing when pharmacogenomic results are required rapidly and testing is reactive – e.g. for warfarin, clopidogrel or aminoglycosides
- Although GLHs will remain the main platform for undertaking genetic testing, there should be careful evaluation of capacity and the ability to use local NHS laboratories to optimise test turnaround times.
- Provide laboratories the freedom to decide which specific technology, platform and analytical workflow to use to deliver pharmacogene panel testing, based on local experience and expertise, test turnaround time and cost, ensuring the highest quality assurance standards.

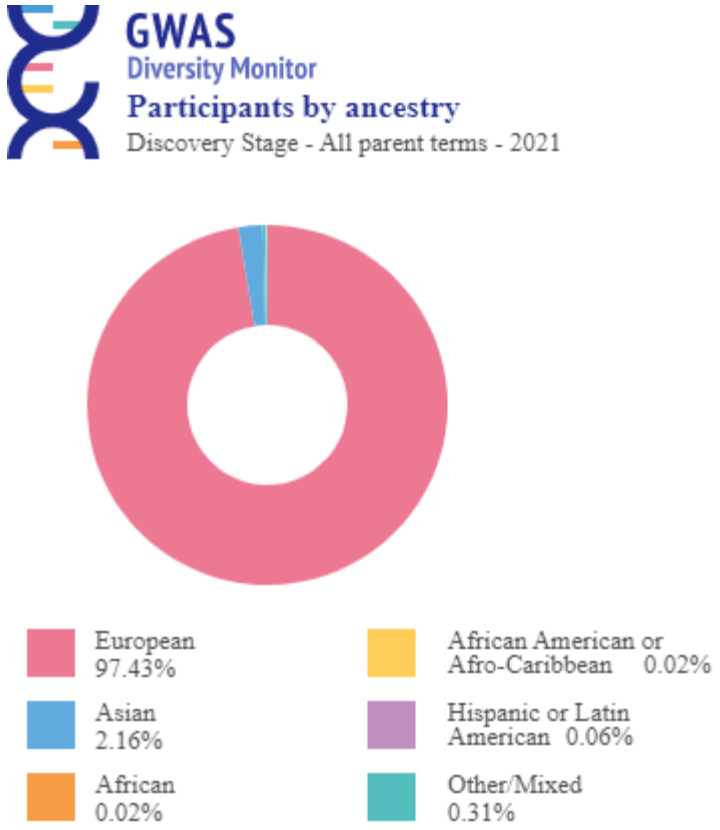
Decision Support Systems

- Develop clinical pharmacogenomics guidance tailored to the NHS
- Develop a report structure that is easy to interpret, strives to avoid user alert fatigue, and contains links to further information (e.g. just-in-time learning resources)
- Develop methods of providing reports across the spectrum of patient record systems, from paper-based to interruptive electronic systems
- Developing coding for genetic variants to allow for incorporation into the EHR.
- Ensure data are stored securely and confidentially
- Build interconnected systems that enable community-based services and hospitals to access clinically relevant pharmacogenomic results for patients
- Future proof the systems so that pharmacogenomic-based recommendations can be added/amended as the research base grows

Education and Training



Lack of Diversity in Genomic Studies

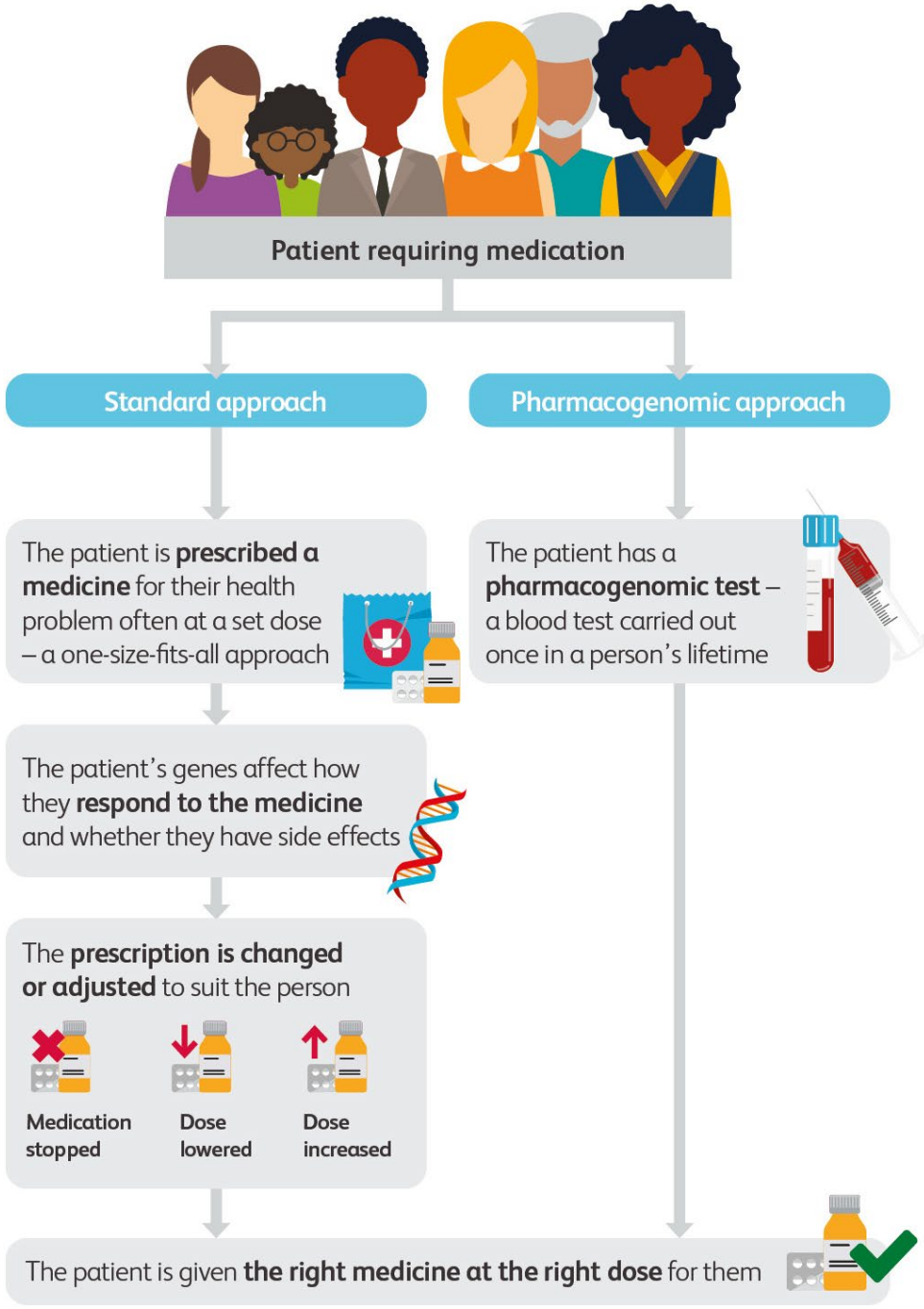


Please cite this as: Mills, M.C and Rahal, C., (2020). 'The GWAS Diversity Monitor Tracks diversity by disease in real time'. Nature Genetics, 52, 242-243. doi: 10.1038/s41588-020-0580-y

13% of people in the UK belong to a Black, Asian, Mixed or other ethnic group

Patients and the Public

The ultimate goal is to make pharmacogenomic prescribing a reality for everyone within the NHS. This will empower healthcare professionals to deliver better, more personalised, care.



Next steps

- Continue engaging with the NHS and the UK Government to make this a reality
- Report has been well received by all bodies and had enormous amount of media interest
- Work with different healthcare professional groups
- Pilot work being undertaken to identify key challenges and develop solutions

- The press release, media briefing and support from a specialist organization resulted in around **600 news articles**.
- Coverage was spread over outlets in **36 different countries**.
- The combined reach of these outlets is estimated at **686 million readers**

Acknowledgements

- The report is dedicated to the memory of Professor Donal O'Donoghue
- Thanks to all the members of the working party and deep dive presenters
- Staff from the RCP and BPS who supported the working party and report production, including Anna Zecharia, Simon Land, Sophia McCully, Charles Whalley, Karen Porter, Jordan Marshall, Janet Leggett-Jones, Dr Norma O'Flynn, Karen Reid and Victoria Wilson.