Pharmacogenomics in the UK National Health Service: Opportunities and Challenges

Authors – Dr Richard Turner, Professor William Newman, Professor Elvira Bramon, Dr Christine j. McNamee, Wai Lup Wong, Dr. Siraj Misbah, Professor Dame Sue Hill, Professor Sir Mark Caulfield, Professor Sir Munir Pirmohamed.

Addresses in short

Dr Richard Turner University of Liverpool, Professor William Newman Manchester University NHS FT, Professor Elvira Bramon University College London, Dr Christine j. McNamee University of Liverpool, Wai Lup Wong University College London, Dr. Siraj Misbah John Radcliffe Hospital Oxford, Professor Dame Sue Hill NHS England, Professor Sir Mark Caulfield Genomics England, Professor Sir Munir Pirmohamed University of Liverpool.

Author for correspondence: Professor Sir Munir Pirmohamed

Keywords: Pharmacogenomics, NHS, clinical practice,

Abstract

There is increasing interest in pharmacogenomics. However, it is also widely acknowledged that implementation of pharmacogenomics into clinical practice has been slow. Implementation is being undertaken in many centres in the US, but this is not nationwide and often focused on highly specialised academic centres, driven by champions. To date, there has been no implementation on a whole country basis. The UK National Health Service (NHS) is a single integrated healthcare system, which provides free care to all patients at the point of need. Recently, there has been a drive to implement genomic medicine into the NHS, largely spurred on by the success of the 100,000 genomes project. This represents an unprecedented opportunity to implement pharmacogenomics for over 60 million people. In order to discuss the potential for implementing pharmacogenomics into the NHS, the UK Pharmacogenetics and Stratified Medicine Network, NHS England and Genomics England invited experts from academia, the healthcare sector, industry and patient representatives to come together to discuss the opportunities and challenges[1]. This report highlights the discussions of the workshop with the aim of providing an overview of the issues that need to be considered to enable pharmacogenomic medicine to become mainstream within the NHS.

Introduction

The UK spends approximately £16.8 billion per year on prescription drugs and this will soon rise to £20 billion, but currently only 50-75% of those drugs prescribed to patients are effective[2]. Ineffective use of drugs, and patients suffering adverse drug reactions (ADRs), place a huge burden on the NHS (and other healthcare systems worldwide) in terms of consumable costs and clinical contact time. ADRs alone account for 6.5% of hospital admissions, and 14.7% of extended hospital stays[3], equating to 8,000 hospital beds being occupied at any one time, at a cost of £2 billion per year. Incorporating pharmacogenomics (the study and clinical application of the genomic determinants of drug response) into the prescribing process has the potential to deliver safer, more effective treatments, at optimal cost, to support the NHS develop the Medicines Value Programme[4].

USING GENOMICS FOR DRUG CHOICE AND DRUG DOSE – IMPLICATIONS FOR THE NHS

Cost effectiveness of Pharmacogenomics

It must be accepted that whole genome sequencing technology is novel, still developing at pace, and coverage of sequencing remains limited in some areas of the genome so the use of pharmacogenomics to determine the drug of choice, and the most effective dose, is not without its challenges[5]. Currently there are only a few genetic variants linked to drug-gene interactions compared to the number of drugs on the market. However, for those patients where sequencing has been part of their diagnosis, pre-emptive genotyping could already guide drug choice for known variants without any additional cost or delay to their treatment. As whole-genome-sequencing becomes ever more affordable, the number of drug-gene interactions identified will steadily increase. Widening “wet lab” testing of patient samples to obtain as much genomic information as possible as samples are routinely processed will be invaluable to obtain the scope of data required to scale up the number of drug-gene interactions identified over the next few years. It may eventually become cost effective to

sequence the genomes of the whole population at a certain age, or at the onset of disease, to guide prescribing their treatment. As sequencing, companion diagnostics and panel tests all become more mainstream, there is the potential for a dramatic paradigm shift in clinical care to include genomic medicine. However, more evidence that pharmacogenomics prescribing improves clinical outcomes is required before its widespread incorporation into patient care becomes reality.

Initially, it may be worthwhile to concentrate on the pharmacogenetics opportunities for the most important drugs, selected by volume of prescription, cost and health burden, and those drugs associated with ADRs or poor efficacy. For example, the IMPACT trial, approved by Health Canada, is analysing how eight genes may affect a patient's metabolism and their response to 33 antidepressant and antipsychotic medications[6]. There is already strong evidence that genetic variants are associated with the development of ADRs[7]. For example, variants in the HLA region on the short arm of chromosome 6 have been linked to off target ADRs in up to 30 different drugs[8]. A clinical study estimated around 80% of healthy volunteers have at least 1 *HLA* risk allele so any multi-gene panel test developed to identify variations in the *HLA* region must be future-proof to incorporate additional variants as they become linked to drug response phenotypes. Evaluating the monitoring of only those patients identified with *HLA* risk alleles for reactions to prescribed drugs associated with rare idiosyncratic immunological ADRs, instead of monitoring all patients prescribed these drugs, would help demonstrate how pharmacogenomics has the potential to reduce the number of clinical appointments by stratifying monitoring. Routinely sequencing patients who have previously experienced an ADR may direct more efficient prescribing for their future treatment.

Evaluating the effectiveness of incorporating genomic medicine into the UK prescribing process will be challenging. Abacavir[9] is often quoted as an exemplar of the cost effectiveness of genomic testing but should be considered an outlier until more evidence of the value of using a pharmacogenomics approach is available. Genetic variants relating to ADRs are not common enough to generate enough data to demonstrate the economic value of pharmacogenomics. Novel study designs will be required to evaluate prescribing decisions based on pharmacogenomics data, as traditional randomized controlled trials will mostly be neither feasible nor appropriate. Recruiting patients into pharmacogenomics Quality Improvement Programs on the day of admission to hospital, or via another randomisation approach, will help determine if prescribing based on genomic medicine delivers any improvements in patient outcome.

Developing pharmacogenomics testing

A genomic diagnostic test must be cost effective, easy to analyse the results, and have suitable support systems in place for clinicians to access and interpret the data, to be of benefit to patients. As our knowledge of drug-gene interactions increases, it will become more likely that pre-emptive array-based technologies will be the most practical in terms of cost, turnaround time, convenience, and capacity to genotype multiple pre-specified variants, rather than analysing single gene sequences. It is also important to consider the context for prescribing the test and processing of results before developing the test. For example, should it be a routine laboratory test with the results reported within a defined period (ideally within

one week) or is there a need for point-of-care (POC) testing in acute settings to provide immediate results?

Efficient test turnaround times will be critical to meet the demands of the proposed model of incorporating reactive pharmacogenomics testing into prescribing. Clinicians do not have the resources to amend existing workflows to recall patients to alter a prescription as additional pharmacogenomics information becomes available. Furthermore, many ADRs occur soon after starting a new drug, and so any delay in test turnaround time could attenuate the positive health impact of utilising pharmacogenomics data in the prescribing process. Incorporating a facility for clinicians to state a timeframe for the patient commencing a drug treatment would help laboratories prioritise their order of sample analysis, and harness existing workflows to deliver results before treatment begins. For instance, widespread pharmacogenomics testing incorporated in routine pre-operative assessment clinics would provide genetic information for post-operative analgesia prescribing for drugs such as codeine. In other cases, such as pharmacogenomics-mediated dosing of warfarin, a POC test would be required to allow clinicians to more accurately prescribe treatment without the need of repeated clinical appointments.

Pharmacogenetics is currently available at specialist research active hospitals in a growing number of countries. The European Ubiquitous Pharmacogenetics consortium (U-PGx)[10] is researching the major challenges / obstacles for the implementation of pharmacogenomics testing in patient care, taking into account the diversity of healthcare systems and citizens across Europe. Specifically, U-PGx is investigating if the emerging approach of pre-emptive genotyping an entire panel of important pharmacogenomics markers is cost-effective and results in a better outcome for patients. The outcome of this initiative, along with other large-scale US projects, will be integral to the ongoing development of the evidence underpinning the value of pharmacogenomics. Furthermore, the rollout of such projects will create the opportunity to build the evidence base for both clinical utility and cost effectiveness of pharmacogenomics prescribing in real world settings. The evidence from these projects will help develop healthcare professionals 'buy in' to establish the routine use of pharmacogenomics in the NHS and other international healthcare systems.

OPPORTUNITIES & CHALLENGES FOR INTRODUCING PHARMACOGENOMICS INTO THE NHS

National genomic testing service

The UK has already made significant investment in genomic medicine by setting up the 100k Genomes Project to aid the diagnosis and potentially the treatment of patients suffering from either previously un-diagnosed rare diseases or cancers[11]. Linking the big data collected from this project, with other initiatives such as the UK Biobank, will offer a way forward to identify variants of clinical relevance. The Genomic Medicine Service[12], an infrastructure of nationwide genomic laboratories that links the Genomic Medicine Centres established for the 100K Genomes Project with other services, such as support from clinical geneticists, has already been set up in England. Patient genomic data held as a single repository will facilitate research into identifying gene-drug interactions and help to establish which interactions will link into the National Genomic Test Registry for the Genomic Medicine Service.

Reconfiguration of national genomic laboratories, and the creation of Sustainability and Transformation Partnerships (STPs) and Integrated Care Services[13] that integrate local primary and secondary care services closer together, are bringing about pronounced changes in the NHS. For example, if a GP requests a pharmacogenomics test that prevents a hospitalisation, the patient and the STP both benefit, rather than it being perceived the GP has had to subsidise the hospital service by carrying out the test. These changes represent clear opportunities to introduce a comprehensive national pharmacogenomics service.

Implementing a genomic service into the NHS

A pragmatic approach that automatically offers genetic testing to patients newly prescribed a drug(s) where there is already a pharmacogenomics clinical guideline available will encourage implementation. The number of headline drug-gene pairs targeted during this early stage of implementation will be dependent on the initial funding allocation given to the rollout of pharmacogenomics across the NHS, and the incidence of prescribing for the chosen therapeutics. NHS England have convened an expert group to review the evidence for known drug-gene associations and to recommend which variants to incorporate into the standardised NHS England test directory. Based on the strength of evidence underpinning their drug-gene associations, and the severity of their associated genotype-influenced ADR(s), the key drugs to consider for the initial test directory should include clopidogrel, codeine, warfarin and 5-fluoropyrimidines. The magnitude of benefit to patients and the NHS will increase as the implementation of genomic medicine occurs across the various therapeutic areas.

As the cost of genotyping additional variants diminishes, adopting a 'test broad-report narrow' approach, whereby common and rare variants in multiple pharmacogenes are simultaneously genotyped but only those variants with the strongest evidence base are reported into the patient's electronic health record, would maximise output. Details of the remaining variants would be stored and released into medical records as evidence for their clinical relevance accrues. This approach would future proof the test and save on costs of re-testing patients as new variants emerge. Decisions on the actual technology utilised for the tests left to the discretion of the provider genomic laboratories would encourage innovation as technologies advance, and accommodate local preferences and expertise.

Far more information on a gene-by-gene basis is required before it is safe to recommend genomic testing follows exclusively either a sequencing or panel approach. In some cases, where multiple functionally relevant rare variants occur in a single gene, sequencing may be required rather than a targeted genotyping approach. For example, whilst array-based genotyping of the 42 known pathogenic *RYR1* variants (associated with malignant hyperthermia, a life threatening reaction to specific anaesthetic drugs) is feasible and sits in a single workflow, sequencing will capture additional rare variants outside the array panel. However, these additional rare variants have uncertain significance and so would not be included in patient's medical records and so would not alter clinical decisions. As an expert group have defined the Standardised National Test Directory (and it is updated annually), any compensation claims brought against the NHS by patients (or others) for not identifying rare variants beyond the directory would be without merit. To mitigate against patient confusion,

the information sheet within the informed consent process could clearly state that the panel test cannot identify every genomic risk or ADR.

Data management and Information technology

Genomic sequencing produces large amounts of complex data, much of which may not be relevant to decisions on patient treatment but has enormous research value. Clinicians require support from specialist bioinformaticians to develop algorithms that identify the clinically actionable genetic variants within sequencing data to incorporate pharmacogenomics routinely into clinical practice. To help clinicians incorporate pharmacogenomics into rational prescribing decisions, Computerised Decision Support Systems (CDSS) that analyse patient's genomic data and flag up any relevant variant-drug interactions are required. These CDSS systems must produce targeted and strictly evidence-based reports to avoid confusion, and ensure only those findings that have sufficient evidence to be clinically actionable for prescribing are reported. Linking the development of multiple research discovery CDSS and implementation platforms together will help to fully utilise all the data sets collected and keep them up to date with advances in real time. It is critical to link these complex, rapidly evolving, systems to patient's electronic medical record data to utilise pharmacogenomics for prescribing in real time. In the short term, key clinically actionable pharmacogenetics findings associated with severe ADRs, could be incorporated in a way similar to the recording of drug allergies on the front page of a person's electronic GP and hospital records. Ultimately, the vision is for support algorithms to interrogate all key clinical parameters influencing drug response (such as BMI, sex, renal and liver function, diagnostic and genomic data embedded in the patient's clinical record) to recommend to the GP, or prescriber, the most appropriate treatment for the individual.

However it must be noted, whilst the majority of primary practices use an electronic prescribing system, only approximately one third of existing NHS hospitals in England use electronic patient health records. Thus, current healthcare records are fragmented and information does not flow consistently between NHS sectors and community pharmacies. For example, information of treatment during a hospitalisation episode can easily become buried and not transferred back into primary care records. Therefore, a national rollout will be required to extend IT capabilities and provide a single source of patient information, visible to all sectors of NHS care providers including community healthcare and pharmacy services. Emphasising the benefits of improving IT and genomics infrastructure within the UK government life Sciences Strategy will gain support to improve the interoperability of healthcare records.

The incorporation of pharmacogenomics data, along with CDSS tools, into a single source of electronic patient information will facilitate the introduction of genomic medicine into routine clinical practice. Ideally, healthcare providers with CDSS should be free to embed the pharmacogenomics data into their local system to provide point of prescribing recommendations on their local prescribing platform to increase usability. However, they must include a mechanism to download updates on the interpretation of pharmacogenomics

variants, and incorporate any new clinical guidelines in a timely fashion. It is especially important to include any new evidence of drug-gene interactions into the records of those patients on long-term medications. The US have been early adopters of pharmacogenomics so learning from their experiences of developing CDSS systems, from both the academic healthcare institutions, and the associated software companies (e.g. Epic, Cerner), will help the UK to develop a suitable system. Approaching data companies, especially large organisations such as Google or Microsoft, to offer their expertise would support the NHS handle such complex big data sets.

Ethical issues including data ownership, secure storage, anonymization, access by health professionals need resolving. The debate continues on whether data should be stored on NHS patient electronic health records, or held by the individual. Smart phones are becoming almost ubiquitous so patient held health record Apps would provide the patient with some control of their data and 'live prescriptions' could be offered to provide a more efficient service. An alternative option would be to provide patients with a plastic card linked to their centralised data records. Large data computing companies will try to implement commercial systems if no decisions on data are forthcoming.

Challenges of implementing pharmacogenomics into the NHS

The NHS is overstretched and currently have over 100,000 staff vacancies. Patients' needs are becoming more complex and clinicians have to deal with multiple conditions during relatively short consultations. It is not clear where staff will find the time to gain training on pharmacogenomics, or the incentive to change their working practice to incorporate genomic medicine. Staff at all levels within the NHS must be encouraged to focus more on the effective use of medicines and take responsibility to ensure patients receive optimised treatment regimens, as currently there are no referral pathways for prescription review in complex patients. Prescribers require simple, clear, clinically relevant information to support the implementation of pharmacogenomics. For example, "this patient is a poor metaboliser of drug x and so requires an increased dose of xmg/day", or "this is a paediatric patient / elderly patient with impaired liver and kidney function and so requires a lower dose". Combining the expertise of the Genomics Testing Service with clinical pharmacologists, pharmacists and the prescribing clinician into a multidisciplinary service team will help to improve patient treatment plans. Once the National Pharmacogenomics Testing Strategy has been determined, incorporating information about adjusting treatment into the British National Formulary (BNF) framework would support prescribing decisions as most clinicians subscribe to the BNF. Specific NICE guidelines would further support the adoption of a national strategy for the introduction of pharmacogenetics.

'First generation' drug-gene tests already available are particularly important to improve the prescribing for patients with complex polypharmacy needs and could be the prototype for implementing pharmacogenomics in the NHS. However, it must be remembered that the implementation of 'first generation' pharmacogenomics tests, such as *CYP2C19* for clopidogrel[14], and *CYP2C9/VKORC1* for warfarin, risks being superseded by the development of new drugs that are less dependent on *CYP* metabolism. Therefore, the opportunity to benefit from this generation of genetic tests may have already passed, but the new drugs are

significantly more costly and so an economic case may be made for continuing with pharmacogenomics testing for drugs like warfarin[15].

Financial support

Where pharmacogenomics is available in routine clinical practice, funding is either by the patient, insurer, or by the national healthcare service of the clinician requesting the test. The full costs of implementing pharmacogenomics testing are difficult to assess and perceived as potentially expensive, even though testing may ultimately produce cost-savings. NHS England ring fenced funding would offer the best value for money and be most equitable for patients. Any eligibility restrictions for patients should be minimised upon service launch but it would be prudent to assess each drug, or group of drugs, and each condition, for the risk of exceptionally large demand occurring to keep the project within scope. Experience in the Netherlands suggests that whilst a gradual growth in demand for pharmacogenomics testing activity year on year might occur there would be no immediate overwhelming demand for tests. Reviewing the eligibility criteria on an annual basis will help prevent large volumes of requests swamping the service and maintain a cost effective service.

Education of patients

The public are already aware of the growing number of direct to consumer genomic testing services, but do not fully appreciate these tests require validation to be clinically relevant. Careful management of public expectations of receiving their prescribed medication based on pharmacogenomics is essential so genomic medicine retains support and does not appear elitist. Patients must understand more research is required to identify drug-gene interactions to encourage them to donate their samples/data. Genomics becoming part of the National Curriculum in schools would help the next generation understand the benefits pharmacogenomics.

Existing genetic counselling services will not have the nationwide capacity to provide patients with an understanding of genomic testing, or to take formal consent from those patients eligible for a national pharmacogenomics programme. In the majority of cases the prescriber, or member of their multidisciplinary team, will be responsible for taking patient consent for testing. As patients gain a better understanding of genomic medicine, and pharmacogenomics becomes analogous to other routine tests, it may be possible that verbal consent alone becomes sufficient and more complicated consent processes become redundant. In the meantime, clinical pharmacologists and pharmacists could provide patients with information on complex molecular and genetic diagnostics tests through an onward referral pathway.

As well as the ‘push’ from Health Education England, a ‘pull’ from the public would aid the understanding of pharmacogenomics. Media support from scriptwriters for popular TV shows including a story involving pharmacogenomics and exploring the relevant issues in dramas would significantly increase awareness. A documentary by leading televisions channels would help educate the public and gain support for the adoption of genomic medicine.

Education and training of practitioners

The cancer field is successfully leading the way with the use of pharmacogenomics without any major concerns about education. However, most NHS clinicians currently lack awareness of how genomic medicine has the potential to improve the treatments they prescribe and so additional education and training is required for some sectors. Junior doctors receive virtually no pharmacogenomics teaching, even as part of their genomics lectures, during their academic studies, which potentially creates a major barrier to pharmacogenomics becoming routine practice. It is essential that there is an assessment of the knowledge base at all levels from undergraduate to post-graduate, and pharmacogenomics becomes part of the medical curriculum, as well as continuing throughout professional development.

Education for clinicians should cover the science underpinning pharmacogenomics, clinical evidence to date, and exemplars of actionable drug-gene associations. Detailed knowledge of the type of variant and biostatistical methods for identifying the variant are not required. However, clinician concerns such as the time burden associated with obtaining consent for a pharmacogenomics test, interpreting the result and conveying the information to the patient should be addressed. For medical students, the national Prescribing Safety Assessment (PSA) examination[16], and potentially a future national medical licensing examination, afford the opportunity to set national standards on pharmacogenomics medical education. Health Education England have developed the Genomics Education Programme with online training packages and MSc qualifications to meet a range of educational needs[17]. The wide range of educational resources available including face-to-face links with local champions, grand rounds etc., and eLearning modules, short podcasts, videos, and infographics etc., all support dissemination of knowledge. Medical academies and the Royal Colleges have an important role to play in the continued training of healthcare professionals. Linking online additional bite size educational material to CDSS pharmacogenomics patient reports would help clinicians keep pace with pharmacogenomics and specifically with developments regarding clinically actionable drug-gene associations.

Explaining pharmacogenomics test results to patients may present new challenges and currently many clinicians will not have the time, knowledge, or confidence to discuss such results with their patients. An accompanying national strategy to improve genomic literacy amongst healthcare professionals will underpin confidence in testing and relieve concerns regarding the consent process. Slow implementation, dealing with single variants initially will give clinicians time to develop their knowledge and counselling skills. The implementation of pharmacogenomics into any healthcare system does not need to be dependent on a single sector, for example medical professionals, but should be developed around multi-disciplinary teams including pharmacists and nurses. This would enable the process of when to order the tests, how to interpret results and when to take a prescribing decision to become seamlessly integrated into current clinical pathways as a normal part of the care of a patient, in the same way as biochemical testing is currently carried out.

CONCLUSIONS

Pharmacogenomics should be able to support the NHS aim to deliver patients more effective and safer drug treatments, but the degree and pace of its implementation and its overall impact on patient outcomes is inextricably interlinked to:

- Genomic tests that deliver timely, user-friendly results
- Comprehensive, interoperable, patient electronic health records
- Sensible algorithms to interrogate patient data
- CDSS linked across research discovery and implementation platforms to facilitate rational prescribing
- Education of patient and healthcare professionals

With the increasing interest in genomics, and the increasing availability of rapid and cost-effective genotyping technologies, introduction of pharmacogenomics for a healthcare system such as the UK NHS, could be seen as the exemplar for world-wide implementation. Of course, there are challenges, but the opportunities far outweigh these challenges.

Disclaimer: The content of this article represents the collective views of the attendees rather than those of any individual organisation represented at the workshop.

REFERENCES

1. http://www.uk-pgx-stratmed.co.uk/index.php/february-2018-workshop-videos Pharmacogenetics in the NHS workshop presentations.

2. Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. *Trends Mol Med* 2001; **7**(5)**:** 201-204.

3. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ*, et al*. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; **329**(7456)**:** 15-19.

4. https://www.england.nhs.uk/medicines/value-programme/ Medicines Value Programme.

5. Relling MV, Evans WE. Pharmacogenomics in the clinic. *Nature* 2015; **526**(7573)**:** 343-350.

6. http://impact.camhx.ca/en/home.php IMPACT trial.

7. Osanlou O, Pirmohamed M, Daly AK. Pharmacogenetics of Adverse Drug Reactions. *Adv Pharmacol* 2018; **83:** 155-190.

8. Fricke-Galindo I, A LL, Lopez-Lopez M. An update on HLA alleles associated with adverse drug reactions. *Drug Metab Pers Ther* 2017; **32**(2)**:** 73-87.

9. Chaponda M, Pirmohamed M. Hypersensitivity reactions to HIV therapy. *Br J Clin Pharmacol* 2011; **71**(5)**:** 659-671.

10. http://upgx.eu Ubiquitous Pharmacogenetics consortium.

11. https://www.genomicsengland.co.uk/the-100000-genomes-project/ 100k Genomes Project

12. https://www.england.nhs.uk/genomics/nhs-genomic-med-service/ NHS Genomic Medicine Service

13. https://www.england.nhs.uk/integratedcare/stps/ Sustainability and transformation partnerships.

14. Saab YB, Zeenny R, Ramadan WH. Optimizing clopidogrel dose response: a new clinical algorithm comprising CYP2C19 pharmacogenetics and drug interactions. *Ther Clin Risk Manag* 2015; **11:** 1421-1427.

15. Burn J, Pirmohamed M. Direct oral anticoagulants versus warfarin: is new always better than the old? *Open Heart* 2018; **5**(1)**:** e000712.

16. Maxwell SRJ, Coleman JJ, Bollington L, Taylor C, Webb DJ. Prescribing Safety Assessment 2016: Delivery of a national prescribing assessment to 7343 UK final-year medical students. *Br J Clin Pharmacol* 2017; **83**(10)**:** 2249-2258.

17. https://www.genomicseducation.hee.nhs.uk/ Genomics Education Programme.