Institution: University of Liverpool

Unit of Assessment: UoA1

Title of case study: Pioneering pharmacogenomics for maximising the benefit:harm ratio of drugs

Period when the underpinning research was undertaken: January 2000 onwards

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	***Role(s) (e.g. job title):***	***Period(s) employed by submitting HEI:***
Prof Sir Munir Pirmohamed	NHS Chair of Pharmacogenetics and David Weatherall Chair of Medicine	1992 onwards
Prof Ana Alfirevic	Chair of Pharmacology and Personalised Medicine and Head, Department Pharmacology and Therapeutics	2006 onwards
Dr Dan Carr	Lecturer in Pharmacology	2005 onwards
Prof Andrea Jorgensen	Professor of Biostatistics	2004 onwards
Prof Dean Naisbitt	Professor of Drug Safety Science	1999 onwards
Dr Richard Turner	Lecturer in Clinical Pharmacology	2017 onwards

Period when the claimed impact occurred: 1st August 2013 – 31 December 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Adverse drug reactions cause approximately 6.5% of hospital admissions in developed countries. They affect 15% of adult and 17% of paediatric inpatients and cost the NHS GBP1,600,000,000 per year. Our research elucidating the genetic basis for adverse drug reactions has led to policy changes benefitting patient health worldwide. We have shown that genotype-guided patient stratification can reduce adverse drug reactions and has economic benefit to healthcare providers. Our studies and expertise on a wide range of drugs have underpinned the development of a pharmacogenomic testing and adoption strategy for genotype-guided drug selection and dosing in the NHS. This was announced in "GENOME UK: The future of Healthcare," in September 2020, a strategy for creating the most advanced genomic healthcare ecosystem worldwide. National roll-out started in October 2020 with genotype-guided testing to reduce the number of severe adverse reactions to the anti-cancer drug 5-fluorouracil.

2. Underpinning research

Our work focuses on safety pharmacogenomics: how variation in the genome affects drug safety. We have identified variation in genes encoding proteins involved in drug metabolism, drug transport and pharmacodynamic drug targets that increase the probability of adverse drug reactions (ADRs). These findings have been developed into clinically tested dosage algorithms that enable cost-effective genotype-guided clinical decision-making. We have developed pathways for implementing pharmacogenomic testing in clinical practice and shown that implementation is cost effective. Here we highlight two specific areas: warfarin and hypersensitivity ADRs.

Warfarin: Warfarin is widely used globally to reduce the formation of blood clots and hence the risk of stroke and heart attack. Warfarin use is particularly high in low and middle-income countries where cost prohibits the use of more-recently developed direct oral anticoagulants (DOACs). Within the UK warfarin is still prescribed for many patients including those with renal impairment, mechanical heart valves, and other contraindications for DOACs. Although warfarin is highly effective, individual dose requirements are difficult to predict, with a 40-fold variation between the highest and lowest doses needed for therapeutic efficacy. Our initial UK studies showed the importance of two genes, CYP2C9 and VKORC1, in determining warfarin dose (2009 – 2010). We developed dosing algorithms, which incorporated CYP2C9 and VKORC1 allelic variants, age and BMI. The dosing algorithms were tested in a multi-centre randomised controlled trial (RCT) led by Liverpool researchers (EU-PACT; 2011). This study showed that genotype-guided dosing was superior to dosing currently used in clinical practice [3.1]. Genotyping was performed on a point-of-care genotyping platform which provided genetic test results in 2 hours. This point-of-care platform has been refined to provide test results in 45 min and in 2017 was implemented in nurse-led UK anticoagulant clinics in a matched cohort study, which replicated the findings of the EU-PACT RCT [3.2].

Hypersensitivity ADRs: Hypersensitivity ADRs can be fatal and cannot be predicted based on the known pharmacology of the drug. These reactions range from carbamazepine-induced Steven's Johnson Syndrome and toxic epidermal necrolysis (mortality up to 30%), where large blisters develop all over the skin and mucous membranes, to liver failure with terbinafine and a dangerous drop in white blood cell count with clozapine.

Hypersensitivity reactions are mediated by the human leukocyte antigen (HLA) system which plays an essential role in recognising 'self' from 'non-self'. Several specific HLA variants predispose patients to these reactions. Some of our earliest work showed that testing for variation in *HLA-B*57:01* prior to prescribing abacavir to HIV patients was both beneficial in preventing hypersensitivity and cost-effective (2004). We have subsequently contributed to discovery and/or evaluation of nine HLA gene-drug pairs associated with hypersensitivity ADRs across a range of organs. For example, in 2011 we showed that *HLA-A*31:01* was a predisposing factor for various hypersensitivity phenotypes in Northern European ancestry populations treated with carbamazepine [3.3]. This has been replicated by many different groups worldwide. We have also identified genetic variants that predispose people to adverse reactions to the drugs nevirapine [3.4], flucloxacillin, amoxicillin, clozapine, anti-thyroid drugs, terbinafine and co-amoxiclav [3.5].

The difficulty in translating genetic laboratory results into actionable clinical decision-making tools is a major barrier to uptake of pharmacogenomic testing. Our findings have been incorporated into Clinical Pharmacogenetics Implementation Consortium Guidelines for drugs including warfarin (2017) and carbamazepine (2017) to help overcome this barrier. Cost-effectiveness is also an important criterion for healthcare providers when implementing a disruptive innovation such as pharmacogenomic testing. We have worked with researchers at Bangor University to show that a GBP50 multi-gene testing panel comprising several HLA alleles (*HLA-A*31:01, HLA-B*15:02, HLA-B*57:01, HLA-B*58:01, HLA-B (158T),* and *HLA-DQB1 (126Q)*) associated with immune-mediated adverse reactions was cost-saving with the probability of cost-effectiveness being 1.0 at a threshold of GBP30,000 per Quality-Adjusted Life Year [3.6].

3. References to the research

3.1. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, Kesteven P, Christersson C, Wahlstrom B, Stafberg C, Zhang JE, Leathart JB, Kohnke H, Maitland-van der Zee AH, Williamson PR, Daly AK, Avery P, Kamali F, Wadelius M, Group E-P. **A randomized trial of genotype-guided dosing of warfarin**. *N Engl J Med* 2013; 369(24):2294-2303. http://dx.doi.org/10.1056/NEJMoa1311386

3.2. Jorgensen AL, Prince C, Fitzgerald G, Hanson A, Downing J, Reynolds J, Zhang JE, Alfirevic A, Pirmohamed M. **Implementation of genotype-guided dosing of warfarin with point-of-**

care genetic testing in three UK clinics: a matched cohort study. *BMC Med* 2019; 17(1):76. http://dx.doi.org/10.1186/s12916-019-1308-7

3.3. McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperaviciute D, Carrington M, Sills GJ, Marson T, Jia X, de Bakker PI, Chinthapalli K, Molokhia M, Johnson MR, O'Connor GD, Chaila E, Alhusaini S, Shianna KV, Radtke RA, Heinzen EL, Walley N, Pandolfo M, Pichler W, Park BK, Depondt C, Sisodiya SM, Goldstein DB, Deloukas P, Delanty N, Cavalleri GL, Pirmohamed M. **HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans**. *The New England journal of medicine* 2011; 364(12):1134-1143. http://dx.doi.org/10.1056/NEJMoa1013297

3.4. Carr DF, Chaponda M, Jorgensen AL, Castro EC, van Oosterhout JJ, Khoo SH, Lalloo DG, Heyderman RS, Alfirevic A, Pirmohamed M. **Association of human leukocyte antigen alleles and nevirapine hypersensitivity in a Malawian HIV-infected population**. *Clin Infect Dis* 2013; 56(9):1330-1339. http://dx.doi.org/10.1093/cid/cit021

3.5. Kim SH, Saide K, Farrell J, Faulkner L, Tailor A, Ogese M, Daly AK, Pirmohamed M, Park BK, Naisbitt DJ**. Characterization of amoxicillin- and clavulanic acid-specific T cells in patients with amoxicillin-clavulanate-induced liver injury**. Hepatology. 2015 ;62(3):887-99. http://dx.doi.org/10.1002/hep.27912

3.6.Plumpton CO, Pirmohamed M, Hughes, DA. **Cost-effectiveness of panel tests for multiple pharmacogenes associated with adverse drug reactions: An evaluation framework.** *Clin. Pharm. Therapeut.* 2018; 105(6);1429 - 1438. http://dx.doi.org/10.1002/cpt.1312

4. Details of the impact

Embedding pharmacogenomics within healthcare systems is essential for saving the lives of patients at risk of an adverse drug reaction (ADR). Implementing genomic testing to prevent ADRs requires: 1) understanding the genetic and physiological basis for ADRs; 2) regulatory approval for test cases; 3) small scale implementation and evaluation; 4) cost-benefit analysis; and 5) development of pathways for wider implementation. Our research has had impact at each of these stages and has underpinned the decision to **roll-out pharmacogenetic testing** for drug-gene pairs in the NHS [5.1]. The first new pharmacogenomic test was rolled out nationally from 1st October 2020. This is for patients prescribed the anti-cancer drug 5-fluorouracil, which can cause serious – and sometimes life-threatening – ADRs in some cases [5.2].

Warfarin pharmacogenomics: from an algorithm to the clinic: We showed that CYP2C9 and VKORC1 allelic variants strongly affect patient response to warfarin and validated our algorithm [3.1] for these and other factors in a randomised control trial. This work was incorporated into **clinical guidelines published by the International *Clinical Pharmacogenetics Implementation Consortium*, and by societies in France, the Netherlands and Canada** [5.3]. We then successfully implemented genotype-guided dosing for warfarin in nurse-led clinics in three sites in North West England [5.4]. The implementation study positively impacted patients. The mean percentage time in warfarin therapeutic range, indicating treatment quality, was 7.5% higher in the implementation group than in the control group. The testing was well received by patients and staff. Our approach will form the framework for introducing genotype-guided dosing through the NHS England Genomic Laboratory Hubs.

Understanding ADRs: the role of HLA*:** Our demonstration in 2004 that genotyping for *HLA-B*57:01* before prescribing abacavir would be cost-effective for the NHS led to implementation of *HLA-B*57:01* genotyping in HIV clinics in the UK from 2006. Prior to introduction of testing abacavir hypersensitivity reactions were seen in approximately 5-7% of HIV patients. A recent meta-analysis of 12 trials with a total of 3063 confirmed *HLA-B*57:01*-negative patients receiving abacavir showed that the hypersensitivity rate had been reduced to 1.3% or less [5.5]. The importance of testing for HLA alleles is also highlighted by the clinical guidelines for carbamazepine, where we showed that *HLA-A*31:01* was associated with hypersensitivity in those of Northern European ancestry. This finding, and those from replication studies in different populations carried out by other groups, has been incorporated **in drug labels in the EU, US and Japan, and both Canada and Switzerland recommend testing for *HLA-A*31:01 before carbamazepine is prescribed [5.6].

***Developing a platform for pharmacogenomic testing*:** Implementation of HLA testing in clinical practice has been limited, in part because single locus tests are costly (>GBP100) and slow (often taking more than two weeks). To overcome this, through NIHR i4i funding, we partnered with **the UK-based small-to-medium enterprise MC Diagnostics to develop a cost-effective, multiplex test** analysing 23 HLA alleles simultaneously. We have also co-developed a web-based decision support system, which can be used prospectively for stratifying patients by risk. MC Diagnostics hold the patent for the panel, with Liverpool receiving royalties, and the HLA genotyping panel received CE marking in March 2019. The HLA genotyping panel has been brought to market and has been successfully established in routine use in two laboratories in the Netherlands (Rotterdam and Leiden). Further uptake has been limited by the impact of COVID-19 on genetic laboratory services [5.7].

***Implementing pharmacogenomic testing in healthcare*:** Our research has been vital in driving forward policy changes globally. In the UK, pharmacogenomics will ultimately impact almost every patient in the NHS. Health economics analysis carried out with colleagues at the University of Bangor showed that the cost-effectiveness of panel-based pharmacogenomic testing, compared with no genetic testing, would be GBP1,239 per quality-adjusted life-year gained and that at we would expect 1 ADR to be avoided for every 10 people tested. An upper bound of 7.5% of patients annually are predicted to be eligible for a pharmacogenetic test, representing up to 400,000 ADRs prevented each year if all tests were taken. **Our data on the burden of ADRs has been used to develop the policy for rolling out pharmacogenomic testing** via the NHS genetic test directory [5.1].

In addition to cost effectiveness, implementing pharmacogenomics requires a structured testing programme. The Pharmacogenetics and Stratified Medicine Network, which we founded in 2010, was instrumental in working with NHS England to define the benefits of pharmacogenomic testing in the UK [5.8]. We subsequently led the working group that has defined up to 40 drug gene-pairs for potential pharmacogenomic testing within NHS genetic laboratories, roll-out of which has been delayed because of the COVID-19 pandemic. **A strategy for embedding pharmacogenomic testing in the NHS was announced by Her Majesty's Government in September 2020** [5.1].

Our expertise was also utilised by the EMA and MHRA by representation on regulatory committees to make changes to the product information for the anti-cancer drug 5-fluorouracil (5FU) [5.9]. **This resulted in the roll-out of a genotyping test for dihydropyrimidine dehydrogenase (DPD) to predict those at risk of severe ADRs to 5FU.** Approximately 3-5% of the European population have a partial deficiency of DPD and complete DPD deficiency is found in approximately 1 in 1000 people. Patients with partial deficiency need a reduced 5FU dose to reduce the risk of ADRs; those with complete deficiency are at risk of life-threatening ADRs and should not be treated with this class of drug. Genotype-guided dosing for 5FU was piloted in Liverpool during July 2020 and launched as a diagnostic service delivered from the North West Genomic Laboratory Hub, Liverpool site, from 1st August 2020. **On 1st October 2020 the MHRA mandated DPD testing prior to 5FU treatment and the service was rolled-out nationally.** During the period from 1st August – 31st December 2020, the North West Genomic Laboratory Hub tested 1586 patients of whom 145 were shown to be at increased risk of an adverse reaction (9.1%). Of these 144 of these were offered a reduced dose of 5FU and the test prevented extreme toxicity occurring in the remaining patient [5.2].

5. Sources to corroborate the impact

5.1 Our work is citied in the UK government pharmacogenomics strategy; Pirmohamed and co-workers' seminal 2004 paper on the prevalence and cost of adverse drug reactions in the NHS is cited on page 22. https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare

5.2 DPD testing for 5-fluorouracil is the first of the new pharmacogenomic tests to be rolled throughout the UK. Letter from the scientific operational director of the North West

Genomic Laboratory Hub outlining the successful roll-out of the DPD testing for patients prescribed 5FU across Greater Manchester, Lancashire and Cheshire and Merseyside.

5.3 University of Liverpool research was incorporated into a range of guidelines for warfarin. Summary of guidelines on warfarin use held at PharmGKB®: https://www.pharmgkb.org/chemical/PA451906/guidelineAnnotation

5.4 Genotype-guided dosing for warfarin was well-received by patients during the pilot project. Patient quote (page 2) “My mum went on warfarin eight months ago and she was back and forward to the clinic at least four times on a weekly basis before they got the dose right whereas I went back just once. The old way of prescribing warfarin is more hit and miss; this is bespoke medication, calculated on my gene type which meant I could go back to work quicker, feeling well enough to go back to normal life. I think this a win-win for me and for the health service." https://www.innovationagencynwc.nhs.uk/media/Downloads/Genotype%20guided%20warfarin%20dosing.pdf

5.5 Report outlining the reduction in adverse reactions to Abacavir due to pharmacogenomic testing. Stainsby et al. Abacavir Hypersensitivity Reaction Reporting Rates During a Decade of HLA-B*5701 Screening as a Risk-Mitigation Measure (2019) Pharmacotherapy 39(1):40-54. https://accpjournals.onlinelibrary.wiley.com/doi/full/10.1002/phar.2196

5.6 University of Liverpool research influenced the use of pharmacogenomic testing for carbamazepine prescription. Summary of label annotations on PharmGKB®: https://www.pharmgkb.org/chemical/PA448785/labelAnnotation

5.7 Our work with MC Diagnostics was beneficial to the company, and has positively impacted pharmacogenomic testing in the Netherlands. Letter from the Founder and Chief Executive Officer of MC Diagnostics outlining the positive impact of collaboration with the University of Liverpool and Bangor University to develop and HLA biomarker panel; and from the head of the IFCC Expert-Center on Pharmacogenetics, Dept. Clinical Chemistry, Erasmus MC University Center, Rotterdam where the panel is in routine use.

5.8 The Pharmacogenetics and Stratified Medicine Network led workshops with NHS England and Genomics England to support implementation. "[In February 2018] 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 of implementing pharmacogenomics into the NHS." https://www.futuremedicine.com/doi/abs/10.2217/pgs-2020-0091 **and with NHS Health Education England to extend the earlier discussions,** "on 22nd May [2019] the [Genomics Education Programme] held a workshop in association with the UK Pharmacogenetics and Stratified Medicine Network to explore the benefits of pharmacogenomics and its status in the NHS." https://www.genomicseducation.hee.nhs.uk/blog/pharmacogenomics-a-new-normal-for-the-nhs/

5.9 In November 2019 Pirmohamed chaired the meeting of the Medicines and Healthcare products Regulatory Agency Pharmacovigilance Expert Advisory Group which carried out the Risk Assessment for 5-Fluorouracil and "considered the appropriate design of potential studies to further monitor patient safety outcomes, the impact of DPD enzyme and the genetic variants, and the impact of DPD screening." https://app.box.com/s/jv487awvqzzsrdql0o34h9gg350ceyd4/file/671748927701