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GUIDELINES

How to assess pharmacogenomic tests for implementation in the NHS in England

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Abstract

Aims: Pharmacogenomic testing has the potential to target medicines more effectively towards those who will benefit and avoid use in individuals at risk of harm. Health economies are actively considering how pharmacogenomic tests can be integrated into health care systems to improve use of medicines. However, one of the barriers to effective implementation is evaluation of the evidence including clinical usefulness, cost-effectiveness, and operational requirements. We sought to develop a framework that could aid the implementation of pharmacogenomic testing. We take the view from the National Health Service (NHS) in England.

Methods: We used a literature review using EMBASE and Medline databases to identify prospective studies of pharmacogenomic testing, focusing on clinical outcomes and implementation of pharmacogenomics. Using this search, we identified key themes relating to the implementation of pharmacogenomic tests. We used a clinical advisory group with expertise in pharmacology, pharmacogenomics, formulary evaluation, and policy implementation to review data from our literature review and the interpretation of these data. With the clinical advisory group, we prioritized themes and developed a framework to evaluate proposals to implement pharmacogenomics tests.

Results: Themes that emerged from review of the literature and subsequent discussion were distilled into a 10-point checklist that is proposed as a tool to aid evidence-based implementation of pharmacogenomic testing into routine clinical care within the NHS.

Conclusion: Our 10-point checklist outlines a standardized approach that could be used to evaluate proposals to implement pharmacogenomic tests. We propose a national approach, taking the view of the NHS in England. Using this approach could centralize commissioning of appropriate pharmacogenomic tests, reduce inequity and duplication using regional approaches, and provide a robust and evidence-based framework for adoption. Such an approach could also be applied to other health systems.

Sonali Sanghvi and Reecha Sofat are the principal investigators of this study.

KEYWORDS
health service, implementation, pharmacogenomics

1 | INTRODUCTION

1.1 | Pharmacogenomics

Pharmacogenomics—the study of the interaction between drugs and the genome—could allow prescribers to target medicines more effectively at those who benefit and to avoid their use in those who could be harmed. Genetic variants can affect pharmacokinetic mechanisms (drug handling), such as drug transport or metabolism, or pharmacodynamic responses (the effect of drugs on their therapeutic target). This can lead either to drug toxicity or lack of efficacy, especially for drugs with a narrow therapeutic range and for prodrugs that rely on pharmacokinetic activation.[1] Commonly used drugs may bring benefits to only a minority of those who take them. For example, approximately 1 in 30 of those taking moderate doses of statins for primary prevention of atherosclerotic cardiovascular disease according to standard guidelines is likely to benefit over 10 years of treatment.[2] In terms of toxicity, adverse drug reactions are linked to 1 in 16 hospital admissions in the UK.[3] Understanding variability in drug response could allow drug treatment to be directed more accurately, and help curb unnecessary spending on medicines, which in the National Health Service (NHS) in England was £20.9 billion in the financial year 2019–20.[4]

1.2 | United Kingdom approach

Genome UK: the Future of Healthcare outlines the UK government's ambitions to develop an evidence-based approach to implementing pharmacogenomics within mainstream healthcare.[5] More recently a joint report from the Royal College of Physicians and the British Pharmacological Society outlines how pharmacogenomics could be made more available in routine health care.[6]

NHS England (NHSE) have established a National Genomic Test Directory (NGTD), which outlines the genomic tests that are funded by the NHS in England.[7] The NGTD currently focuses on cancer and rare diseases, and includes four pharmacogenomic that test for four variants including the dihydropyrimidine dehydrogenase gene (*DPYD*) for fluoropyrimidines (Box 1), a mitochondrial *RNR1* test for aminoglycoside antibiotics (Box 5) and *TPMT* and *NUDT15* for purine analogue drugs.[7] This repertoire of tests may expand with NHSE plans to establish a pharmacogenomic test evaluation group.

NHSE have outlined a scoring framework and process by which test evaluation working group members can assess any genomic test for addition to the NGTD.[9] However, the information available to members to support this scoring process is unclear. Pharmacogenomic testing differs from many existing genomic tests in the

What is already known about this subject

- Pharmacogenomic testing has the potential to target medicines more effectively towards those who will benefit and avoid use in individuals at risk of harm.
- Health economies are actively considering how pharmacogenomic tests can be implemented into healthcare systems to make better use of medicines.
- One of the barriers for implementation is evaluation of the evidence including clinical usefulness, cost-effectiveness and operational requirements.

What this study adds

- We provide a framework that could aid the implementation of pharmacogenomic testing.
- We take the view from the National Health Service in England, although this framework could be applied more generally.
- We propose a centralized commissioning model that aims to reduce inequity and duplication but remain transparent and evidence-based.

BOX 1 Fluoropyrimidines and *DPYD*.

Fluoropyrimidine chemotherapies such as 5-fluorouracil and capecitabine are commonly used in cancer regimens. Variants in the *DPYD* gene reduce the activity of the enzyme dihydropyrimidine dehydrogenase that inactivates fluoropyrimidine, and so put patients at risk of toxicity from high drug concentrations. In 2020, NHSE commissioned a combined pharmacogenomic test for 4 variants, estimated to predict 20–30% of early-onset life-threatening 5-fluorouracil toxicities.[8]

NHSE supported implementation of the DPYD testing it commissioned through the network of seven Genomic Laboratory Hubs in England and, with the UK Chemotherapy Board, provided clinical guidance to support test interpretation. It also commissioned work to assess equity of access to testing, creation of a clinical registry and identification of additional DPYD variants relevant to patients of different ethnicities. This underlines the complexities of implementing pharmacogenomic testing and provides a potential blueprint for future pharmacogenomic tests.

FIGURE 1 Checklist for assessing pharmacogenomic tests for implementation.

1. Is there robust evidence of a drug-gene pair association?
2. Is there evidence from well-designed controlled trials that the pharmacogenomic test improves clinical outcomes?
3. Does the addition of the pharmacogenomic test improve clinical effectiveness (real world outcomes)?
4. Is there clinical guidance available to support interpretation of pharmacogenomic test results?
5. Which patients should be tested and by whom?
6. Are alternative therapeutic options available that may affect the treatment pathway?
7. What is the testing approach and does this fit with the clinical pathway?
8. Is the pharmacogenomic test cost-effective and affordable?
9. Are any operational changes required to implement testing?
10. How will the impact of the pharmacogenomic test be evaluated?

requirements for implementation and impact. It is potentially applicable to all prescribers, in multiple professions, specialties and sectors. The demonstration of a link between a genomic variant and the safety or efficacy of a drug treatment is only the first step in deciding whether prospective testing would yield a *clinically actionable* result[10] for the individual as well as being cost-effective at a population level.

Here, we outline a framework that can be used by health care systems and commissioners to assess pharmacogenomic tests proposed for implementation. The current NGTD process is a positive first step but can be further developed by including these pharmacogenomic-specific considerations and adopting the gold standard evaluation methodology used by the National Institute for Health and Care Excellence (NICE).

We further present a proposed model for national assessment of pharmacogenomic testing for the NHS.

2 | METHODS

We identified the themes of this framework after a literature search of EMBASE and Medline databases to identify prospective studies of pharmacogenomic testing focusing on clinical outcomes, and key studies on the mainstream implementation of pharmacogenomics. We considered both efficacy (clinical trial evidence) and effectiveness (clinical usefulness in the real world). We use the term clinical usefulness to mean the extent to which a test reduces clinical uncertainty, influences clinical decisions, improves outcome, provides benefit greater than established measures and is generalizable.[11] We distinguish this from utility in the health economic sense, which is commonly measured in quality-adjusted life years (QALYs), "calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale)."[12] By cost-effectiveness we mean the value for money, represented, for example, by the cost per QALY. We discussed these themes and developed this pragmatic framework of general principles. We formed a clinical expert advisory group by invitation of clinicians with expertise in pharmacology, pharmacogenomics, formulary evaluation and policy implementation who we knew through existing professional relationship. Our group held a series of online meetings to review the data from the literature search, prioritize themes and inform interpretation of the data, and developed this pragmatic framework of general principles.

3 | RESULTS

Themes that emerged from the discussions of the clinical advisory group are distilled as 10 questions. These provide a framework for evaluation of pharmacogenomic tests for clinicians and policy groups seeking to implement such tests. These are set out as below (Figure 1).

3.1 | Is there robust evidence of a drug–gene pair association?

There are published, evidence-based, peer-reviewed guidelines of drug–gene pairs for which the pharmacokinetic or pharmacodynamic association is robustly established via biomedical research studies.[13,14] One set of guidelines advises how best to prescribe for patients of known genotype.[13] The other indicates which drugs suggest or mandate patient genotyping before prescribing—a more relevant consideration in the NHS at present.[14] The PharmGKB database lists 34 drugs whose European Medicines Agency (EMA) licences include *actionable* pharmacogenomic information, but pharmacogenomic testing has only been adopted into clinical practice for a few of these drugs.[15] Assessments of clinical usefulness and health economic utility are both necessary for effective implementation into practice.

3.2 | Is there evidence in well-designed controlled trials that the pharmacogenomic test improves clinical outcomes?

Having established that variants in a specific gene affect a particular drug, the next step is to assess whether prospective pharmacogenomic information will improve its efficacy or safety. Ideally, this should be based on clinical outcomes rather than biomarkers alone. Subsequently, the effectiveness of pharmacogenetic testing in clinical practice will need to be established.

Prospective randomized controlled trials in pharmacogenomics have proven challenging and costly, particularly for low prevalence variants that require large studies to reach adequate power. Ethnic differences in the prevalence of pharmacogenomic variants can also affect power calculations and the applicability of results.[16] Despite these challenges, robust randomized controlled trials in pharmacogenomics have emerged over the last decade, made more feasible by the falling cost of genotyping and multicentre collaborative approaches (see Box 2).[17–25] PREPARE, a randomized open-label multicentre European study published in 2023, examined the effect of screening for a panel of 12 genes in nearly 7000 patients who were to be prescribed one of the drugs whose adverse effects were likely to be related to one of the 12 genes. The primary analysis showed a significant reduction in adverse reactions to the drug for which the test was performed (odds ratio 0·70 [95% CI 0·54–0·91]; $P = .0075$). However, the odds ratio was unchanged by testing for the other 11 genes (odds ratio 0·69 [95% CI 0·61–0·78]). The study concluded that, while feasible, challenges to wide-spread use of panel screening remained.[26] We agree that, even if testing for a relevant gene (or, rarely, genes) prior to treatment with a specific drug can be clinically useful, there is, up to now, no good evidence to support the clinical usefulness or cost-effectiveness of panel screening.

It will be important to implement tests that show demonstrably better patient outcomes or clinical pathways for clinicians, patients and policymakers to be confident in the adoption of pharmacogenetic testing, and ensure cost-effective use of NHS resources.

3.3 | Does the addition of the pharmacogenomic test improve clinical effectiveness (real-world outcomes)?

Pharmacogenomics is just one of many factors that determine an individual's drug response. Other important considerations include dose, age, sex, physiological factors such as pregnancy, exogenous factors such as diet or drugs, and diseases such as liver disease.[27]

Up to now, few studies have evaluated whether implementation of genetic testing before starting treatment is both clinically useful and cost-effective. Our view is that such evaluation is necessary if a test is to be adopted widely in a financially constrained healthcare system. This might mean that the evidence threshold for implementation of pharmacogenomic testing is significantly higher than for other tests that guide therapeutic decisions.[28,29] For example, dosage adjustment in impaired kidney function has often been based on theoretical pharmacokinetic calculations rather than outcome data. However, studies demonstrate significant unwarranted variation and excessive use of non-genetic testing, which may contribute to patient harm and escalating costs, so this approach should not be regarded as a standard of best practice.[30,31]

For a pharmacogenomic test to be clinically useful, it should provide additional benefit to other factors known to affect treatment choice and drug response.

Algorithms to support treatment decisions for drugs with complex dose–response relationships, like tacrolimus (Box 3), would need to incorporate genomic, clinical and demographic factors.

BOX 2 Abacavir and *HLA-B*5701*.

The landmark study by Mallal *et al.*[17] was the first to show clinical usefulness of a pharmacogenomic test for the antiretroviral drug abacavir. The study demonstrated that pharmacogenomic testing for the *HLA-B*5701* allele prior to initiating abacavir therapy eliminated cases of immunologically confirmed hypersensitivity reactions compared to not testing (0% *vs*. 2.7%; $P < .001$). The study is an example of a gold standard pharmacogenomic study, with a robust, double-blind, randomized trial design, a patient-focused outcome, multisite international collaboration representing different ethnicities and adequate power to detect a significant difference. Pharmacogenomic testing for *HLA-B*5701* has since been implemented across the NHS and is mandated within the drug licence.

BOX 3 Tacrolimus and *CYP3A5*.

The optimal dose of the immunosuppressant drug tacrolimus depends on several factors, including age, concomitant medication, liver function, ethnicity and genotype: *CYP3A5* gene variants influence dose-adjusted concentrations of tacrolimus.[32] However in studies of the clinical usefulness of genotype-guided dosing for tacrolimus, only around 40% of patients reached therapeutic range at steady state,[21,22] and reductions in clinical outcomes such as graft loss, acute rejection or adverse events were not observed.[22,33] Routine prospective pharmacogenomic testing may not improve treatments where therapeutic drug monitoring is already embedded.

Patient adherence to treatment is another major determinant of response; it may be as low as 50% for antihypertensive medicines.[34] For the drug simvastatin, patients with loss-of-function variants in the *SLCO1B1* gene are more likely to suffer muscular adverse effects, and to stop treatment. However, genotype-guided recommendation did not improve statin adherence compared with usual care in patients who had stopped statin treatment because of adverse drug reactions (ADRs).[35] This suggests that patients should be aware of pharmacogenomic tests and confident that they are reliable, if testing is to be implemented effectively.

3.4 | Is there clinical guidance available to support interpretation of pharmacogenomic test results?

Clinical recommendations for interpreting pharmacogenomic test results should be incorporated into standardized test report templates from genetic testing laboratories, so that clinicians can translate the result into an appropriate clinical decision. Actions may include dose adjustment, increased monitoring, or selection of an alternative treatment. Clinical Pharmacogenetics Implementation Consortium and Dutch Pharmacogenetics Working Group clinical guidelines contain evidence-based recommendations for interpretation and dose adjustment.[13,14] These interventions need to be considered in the context of the clinical pathway and may need to be modified to allow for international differences in clinical practice and available treatments.

3.5 | Which patients should be tested and by whom?

Before pharmacogenetic tests are adopted, it is necessary to identify the criteria by which to judge whether a pharmacogenomic test will be clinically and cost-effective, and thereby define the patient cohort who should receive the test. Key factors include the suggested clinical action where a variant is detected, effect on patient outcomes, availability of alternative therapeutic options, feasibility of testing within clinical practice, test turnaround time, estimated testing volume and cost of implementation. The criteria for adopting prospective pharmacogenetic testing should be analogous to other tests for screening patients at risk.[36]

Some pharmacogenomic tests are proven to prevent serious and life-threatening ADRs (Boxes 1 and 2). Where the clinical usefulness of a test is less certain, further studies and careful analysis of the groups most likely to benefit will be needed.

Variation in prevalence and effect of pharmacogenomic variants in different populations and ethnicities is also an important consideration. For example, *HLA-B*5801* predicts severe cutaneous adverse reactions to allopurinol, but the genotype is 10 times more common in Asian than European populations[37]; and *HLA-B*1502* increases the risk of toxic epidermal necrolysis with carbamazepine in Chinese populations,[38] but in Japanese and European populations *HLA-A*3101* is more important.[39,40] Many ethnic groups are also underrepresented in the clinical databases and research studies that inform implementation. It is vitally important that pharmacogenomic tests are applied equitably across populations to avoid introducing further health inequalities.

Testing criteria should also define the healthcare professionals who can order the test to enable targeted training, embedding of testing into the relevant clinical pathway and appropriate test ordering.

3.6 | Are alternative therapeutic options available that may affect the treatment pathway?

When pharmacogenomic testing contraindicates use of a drug, the overall clinical benefit depends on the availability, safety, efficacy and cost-effectiveness of alternative treatments. Where no safe, cost-effective alternative exists, the patient and clinicians must weigh the potential harm of prescribing against that of denying treatment. The analysis must consider the robustness of evidence supporting the pharmacogenetic test. Gene variants often cause a spectrum of effects, while test results may be dichotomized as positive or negative. For example, defining a threshold for *poor metabolizers* may make tests easier to interpret, but oversimplify assessment and deny patients potentially beneficial treatments.[1]

Changes in treatment pathways as new drugs and evidence emerge requires a dynamic approach to implementation and re-evaluation of clinical usefulness (Box 4).

BOX 4 Warfarin and *CYP2C9* and *VKORC1*.

Warfarin is one of the most-studied examples of pharmacogenomic testing. Variants in several genes, notably *CYP2C9* and *VKORC1*, influence warfarin dose requirements. Genotype-guided warfarin therapy is reported to improve the time in therapeutic range compared to standard dosing (mean difference 3.41%; 95% CI 0.71–6.10%; $P = .01$).[41]

However, as more patients switch from warfarin to direct oral anticoagulant alternatives, with fixed dosing and less need for monitoring, testing for pharmacogenetic influences on warfarin will be a diminishing priority.

3.7 | What is the testing approach and does this fit with the clinical pathway?

Analytical and clinical validity are essential pillars for implementation of genetic testing.[42] An understanding of the testing and technology approach is important for determining cost-effectiveness and feasibility of obtaining timely results within the clinical context.

Tests targeted at specific genes or mutations have been the mainstay technology for assessing the clinical usefulness and decisions on clinical implementation of pharmacogenomic testing before instituting treatment. These tests are faster, cheaper and more widely available than next-generation sequencing. Turnaround times for tests depend on the technology used and can vary from 30 min for point of care testing, up to six weeks for whole genome sequencing.[6] Polymerase chain reaction, loop-mediated isothermal amplification and other gene-targeted technologies allow rapid testing for one or a small number of mutations. Gene panels that enable simultaneous testing for a range of pharmacogenomic targets have also been popular.[6]

The choice of technology must also align with the clinical pathway so that test results are available when needed, to guide decision-making without causing harmful delays to treatment (Box 5).

BOX 5 Gentamicin and m.1555A>G.

Aminoglycoside antibiotics such as gentamicin are used first-line to treat sepsis in neonates. Aminoglycoside-induced hearing loss is strongly associated with the m.1555A>G mutation and has a reported prevalence of ~0.2% (1 in 500).[43]

Traditional genotyping assays take 3–4 days to return a result, but antibiotics for suspected sepsis must be delivered within 1 h. The PALOH study showed that a point of care test administered by clinical ward staff was feasible within the neonatal setting, with a turnaround time of less than 30 min. Genotype was used to guide antibiotic prescription without disrupting safe clinical practice.[43]

3.8 | Is the pharmacogenomic test cost-effective and affordable?

The appraisal of a pharmacogenomic test should include measures of cost-effectiveness. Cost-effectiveness analyses of pharmacogenomic tests weigh up the value of testing according to health improvements against costs, and, like medicines, can be compared by using cost per QALY measures. These analyses must be assessed to ensure they are unbiased, relevant and consider key factors such as alternative treatments, rarity of outcome and cost of testing.[44]

To date, cost-effectiveness studies have typically been limited to single drug–gene pairs associated with common but serious ADRs, such as HLA-testing for abacavir.[45] Testing a multigene pharmacogenomic panel has been proposed to be more cost-effective in the long-term. Kimpton *et al.*[46] reported that, over a 5-year period, nearly half of patients aged 50–99 years would be expected to be prescribed 2 or more drugs associated with *actionable* pharmacogenetic variants. A panel approach to testing could inform prescribing decisions over a patient's lifetime but may be limited by lack of an interoperable patient record, the emergence of new treatments and evolving evidence on pharmacogenomic variants. While panel testing provides pharmacogenomic information for multiple treatments, it will be limited if the evidence for some included variants is weak. In some instances, genotyping will be less useful or less cost-effective than phenotyping.[47,48] The challenge of effectively interpreting results and communicating genetic risks to both clinician and patient is also amplified.

There are some circumstances where different genotypes pose competing risks for different agents with similar actions. For example, serum concentrations of all common statins are higher in homozygotes for *SLCO1B1*14*, for fluvastatin are higher in homozygotes for *CYP2C9*3* and those with *ABCG2 c.421 A/A* have higher concentrations of rosuvastatin.[49] In these cases, limited panel testing would make clinical sense if there was clear evidence that increased concentrations of statin in those with genetic variants translated into significant risk of unacceptable harm.

Many potential pharmacogenomic tests are for inexpensive medicines commonly prescribed in both primary and secondary care settings, such as antidepressants and opioids, and for which clinical strategies for dose adjustment mitigate harm. The potential volume of testing for these common drugs would be costly. This highlights the requirement to establish clear testing criteria.

3.9 | Are any operational changes required to implement testing?

Pharmacogenomic testing can only be integrated into clinical pathways if scientific, laboratory and clinical teams collaborate to overcome operational barriers. For example, long laboratory turnaround times and inadequate resources to interpret and return the results can impede adoption. To achieve the benefits of *personalized care*, clinicians need to know when pharmacogenomic testing is appropriate, be confident in interpreting results and able to discuss the risks and benefits and the alternative treatment options with patients.[6]

The large and rapidly increasing knowledge base for pharmacogenomics means that the introduction must be supported by evidence-based clinical guidelines. Ideally, decision support will be integrated with the patient health record. Effective transfer of pharmacogenomic results across primary and secondary care records requires a single recognized pharmacogenomic information standard, adopted by all users. The Professional Record Standards Body have set out guidance on communicating pharmacogenomic information across patient records and via alerts.[50]

Challenges to implementation differ according to clinical setting. In outpatient and primary care settings, the ability to interpret and discuss pharmacogenomic results with a patient may be limited by the appointment time available. Tools to support patient understanding of pharmacogenomics and genetic risk can aid this shared decision-making process. Follow-up services and expert advice from multidisciplinary teams are needed for effective pharmacogenomics implementation.[6]

BOX 6 Carbamazepine and *HLA-B*1502*.

Even with robust studies of clinical usefulness, unintended consequences can arise as implementation moves from a controlled study environment into clinical practice. A population cohort study found prospective screening of the *HLA-B*1502* genotype prior to initiating patients on carbamazepine eliminated cases of drug-induced Steven–Johnson syndrome and toxic epidermal necrolysis (SJS-TEN).[38] Routine pharmacogenomic screening for carbamazepine was subsequently implemented across the healthcare system in Hong Kong.

However, a real-world analysis in 2014[51] found no overall benefit in reducing SJS-TEN induced antiepileptic drugs with the introduction of routine *HLA-B*1502* screening (0.09 *vs.* 0.07%; $P = .24$). While incidence of carbamazepine-induced SJS-TEN fell from 0.24 to 0%, prescribing of carbamazepine declined. Instead, prescribers opted for alternative antiepileptics that did not require screening, and the incidence of phenytoin-induced SJS-TEN rose from 0.15 to 0.26%.

3.10 | How will the impact of the pharmacogenomic test be evaluated?

Clear pharmacogenomic data standards will enable linking of laboratory and clinical datasets to measure the impact of pharmacogenomic testing over time, because clinical pathways and treatment decision-making are complex, variable and continuously evolving. Because the evidence on new variants is accumulating rapidly, evidence acquired at a single time-point may not achieve optimal benefit from pharmacogenomics and reporting to clinicians and patients needs to be revised as evidence evolves. Ongoing evaluation of prescribing behaviours and outcomes is also needed, to detect unanticipated consequences of pharmacogenomic testing (Box 6).

4 | DISCUSSION

Our view is that a structured approach should be taken to the assessment and governance of pharmacogenomic testing at a national, regional and local level, to ensure equitable access and reduce duplication (see Figure 2). The existing structure for medicines offers a good template for pharmacogenomic testing. For medicines, NICE provide independent expertise in health technology appraisal and cost-effectiveness analysis to produce recommendations for adoption by the

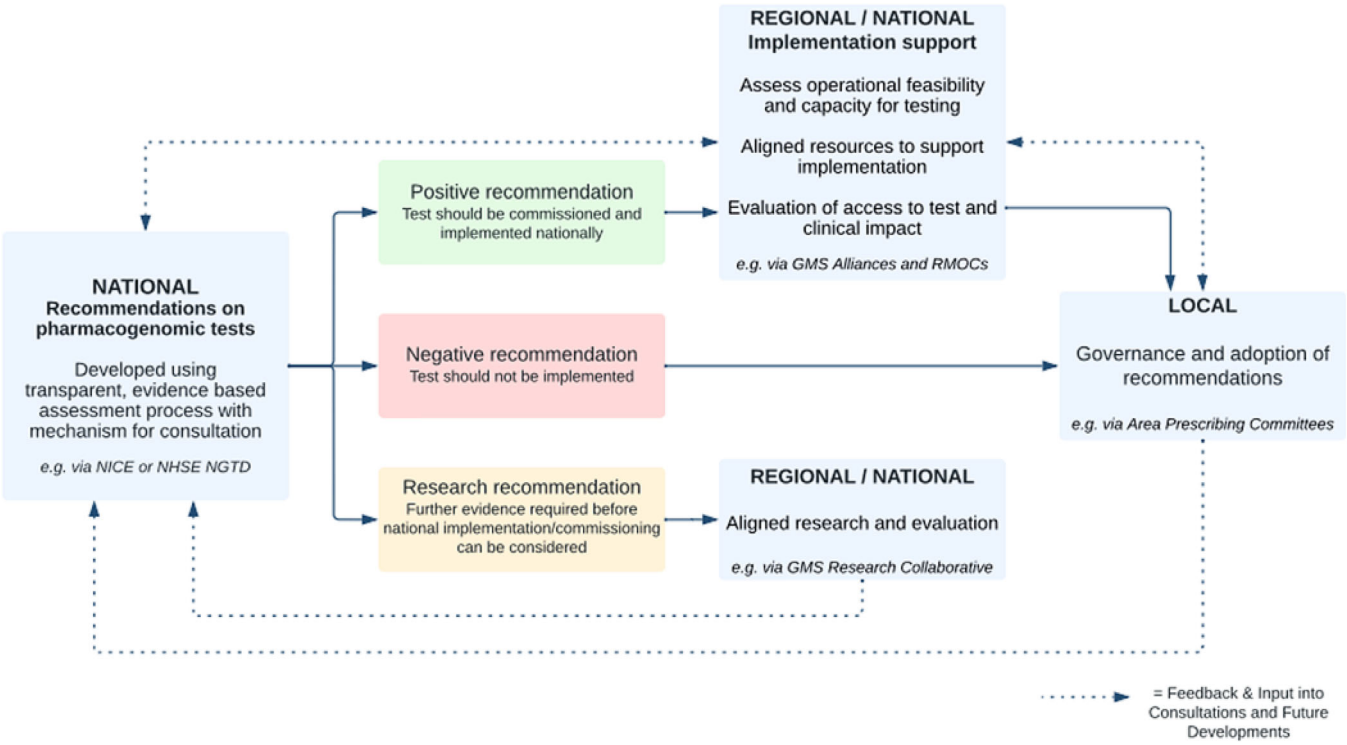

FIGURE 2 Proposed model for the assessment, implementation and governance of pharmacogenomic tests in the NHS. GMS, genomic medicine service; NGTD, National Genomic Test Directory; NHSE, NHS England; NICE, National Institute for health and care excellence; RMOCs, regional medicines optimization committees.

NHS. Area Prescribing Committees and Drugs and Therapeutic Committees support local implementation of the guidelines.

Processes for central evaluation of genomic testing have started to be developed by NHSE via the NGTD.[7] These should further evolve to build on the gold standard evaluation methodology developed by NICE, with transparent methodology and incorporation of an independent analysis of the evidence, budget impact and pharmacogenomic-specific considerations highlighted within this review.

5 | CONCLUSION

Pharmacogenomic testing has the potential to improve treatment efficacy and safety. Implementation of testing into routine practice across a healthcare system will require careful consideration of the evidence, clinical usefulness, cost-effectiveness and operational requirements. Our 10-point checklist outlines a standardized approach to evaluating applications to implement a pharmacogenomic test. A national approach to providing pharmacogenomic test recommendations and centralized commissioning will reduce inequity and duplication, but this process should be clearly set out, transparent, evidence-based, inclusive of the views of stakeholder and supported by appropriately skilled local teams to oversee implementation and monitor use of the tests in practice.

AUTHOR CONTRIBUTIONS

Sonali Sanghvi and Reecha Sofat conceived the paper. Sonali Sanghvi conducted the literature search which formed the basis of the proposed framework and wrote the first draft. All authors reviewed and edited the manuscript. Reecha Sofat is guarantor of the paper.

CONFLICT OF INTEREST STATEMENT

All authors have completed the ICMJE uniform disclosure form and declare the following: A.D.H. sits on the Wellcome Trust Genetics and Genomics Advisory Group. S.S. was previously employed as pharmacy advisor in the Genomics Unit at NHS England. R.S. is a member of the NHS England Genomics Clinical Advisory Group. All other authors have no relevant conflicts to declare.

DATA AVAILABILITY STATEMENT

n/a.

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REFERENCES

1. Roden DM, McLeod HL, Relling MV, et al. Pharmacogenomics. *The Lancet*. 2019;394(10197):521-532. doi:10.1016/S0140-6736(19)31276-0
2. Mortensen MB, Nordestgaard BG. Statin use in primary prevention of atherosclerotic cardiovascular disease according to 5 major guidelines for sensitivity, specificity, and number needed to treat. *JAMA Cardiol*. 2019;4(11):1131-1138. doi:10.1001/jamacardio.2019.3665
3. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ*. 2004;329(7456):15-19. doi:10.1136/bmj.329.7456.15
4. NHS Digital. Prescribing costs in hospitals and the community 2019-2020 [Internet]. Accessed May 4, 2022. https://digital.nhs.uk/data-and-information/publications/statistical/prescribing-costs-in-hospitals-and-the-community
5. GOV.UK. Genome UK: the future of healthcare [Internet]. Accessed May 4, 2022. https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare
6. Royal College of Physicians and British Pharmacological Society. Personalised prescribing: using pharmacogenomics to improve patient outcomes [Internet]. London: RCP and BPS; 2022 Accessed March 5, 2022. https://www.rcp.ac.uk/projects/outputs/personalised-prescribing-using-pharmacogenomics-improve-patient-outcomes
7. NHS England. National genomic test directory [Internet]. Accessed April 20, 2023. https://www.england.nhs.uk/publication/national-genomic-test-directories/
8. NHS England. Clinical commissioning urgent policy statement: pharmacogenomic testing for DPYD polymorphisms with fluoropyrimidine therapies [Internet]. Accessed May 4, 2022. https://www.england.nhs.uk/publication/clinical-commissioning-urgent-policy-statement-pharmacogenomic-testing-for-dpyd-polymorphisms-with-fluoropyrimidine-therapies/
9. NHS England. National genomic test directory: supporting material [Internet]. Accessed May 18, 2022. https://www.england.nhs.uk/publication/national-genomic-test-directory-supporting-material/
10. Liu D, Olson KL, Manzi SF, Mandl KD. Patients dispensed medications with actionable pharmacogenomic biomarkers: rates and characteristics. *Genet Med*. 2021;23(4):782-786. doi:10.1038/s41436-020-01044-2
11. Hornberger J, Doberne J, Chien R. Laboratory-developed test—SynFRAME: an approach for assessing laboratory-developed tests synthesized from prior appraisal frameworks. *Genet Test Mol Biomarkers*. 2012;16(6):605-614. doi:10.1089/gtmb.2011.0177
12. NICE glossary. Accessed May 19, 2023. https://www.nice.org.uk/glossary
13. CPIC. Clinical Pharmacogenetics Implementation Consortium [Internet]. Accessed September 15, 2020. https://cpicpgx.org/
14. DPWG Dutch Pharmacogenetics Working Group (DPWG). [Internet]. Accessed September 15, 2020. https://www.knmp.nl/patientenzorg/medicatiebewaking/farmacogenetica/pharmacogenetics-1/pharmacogenetics
15. Drug Label Annotations [Internet]. PharmGKB. Accessed October 21, 2020. https://www.pharmgkb.org/labelAnnotations
16. White C, Scott RJ, Paul C, Ziolkowski A, Mossman D, Ackland S. Ethnic diversity of DPD activity and the DPYD gene: review of the literature. *Pharmgenomics Pers Med*. 2021;14:1603-1617. doi:10.2147/PGPM.S337147
17. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579. doi:10.1056/NEJMoa0706135
18. Newman WG, Payne K, Tricker K, et al. A pragmatic randomized controlled trial of thiopurine methyltransferase genotyping prior to azathioprine treatment: the TARGET study. *Pharmacogenomics*. 2011;12(6):815-826. doi:10.2217/pgs.11.32
19. Coenen MJH, de Jong DJ, van Marrewijk CJ, et al. Identification of patients with variants in TPMT and dose reduction reduces hematologic events during thiopurine treatment of inflammatory bowel disease. *Gastroenterology*. 2015;149(4):907-917.e7. doi:10.1053/j.gastro.2015.06.002

20. Pereira NL, Farkouh ME, So D, et al. Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. *JAMA*. 2020;324(8):761-771. doi:10.1001/jama.2020.12443
21. Thervet E, Loriot MA, Barbier S, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. *Clin Pharmacol Ther*. 2010;87(6):721-726. doi:10.1038/clpt.2010.17
22. Shuker N, Bouamar R, van Schaik RHN, et al. A randomized controlled trial comparing the efficacy of *Cyp3a5* genotype-based with body-weight-based tacrolimus dosing after living donor kidney transplantation. *Am J Transplant*. 2016;16(7):2085-2096. doi:10.1111/ajt.13691
23. Pirmohamed M, Burnside G, Eriksson N, et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med*. 2013;369(24):2294-2303. doi:10.1056/NEJMoa1311386
24. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med*. 2013;369(24):2283-2293. doi:10.1056/NEJMoa1310669
25. Gage BF, Bass AR, Lin H, et al. Effect of genotype-guided warfarin dosing on clinical events and anticoagulation control among patients undergoing hip or knee arthroplasty: the GIFT randomized clinical trial. *JAMA*. 2017;318(12):1115-1124. doi:10.1001/jama.2017.11469
26. Swen JJ, van der Wouden CH, Manson LE, et al. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. *The Lancet*. 2023;401(10374):347-356. doi:10.1016/S0140-6736(22)01841-4
27. Ferner R, Aronson J. Susceptibility to adverse drug reactions. *Br J Clin Pharmacol*. 2019 Oct;85(10):2205-2212.
28. Schünemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ*. 2008;336(7653):1106-1110. doi:10.1136/bmj.39500.677199.AE
29. Dhanda D, Guzauskas G, Carlson J, Basu A, Veenstra D. Are evidence standards different for genomic- vs. clinical-based precision medicine? A quantitative analysis of individualized warfarin therapy. *Clin Pharmacol Ther*. 2017;102(5):805-814. doi:10.1002/cpt.663
30. O'Sullivan JW, Heneghan C, Perera R, et al. Variation in diagnostic test requests and outcomes: a preliminary metric for OpenPathology.net. *Sci Rep*. 2018;8(1):4752. doi:10.1038/s41598-018-23263-z
31. Whiting D, Croker R, Watson J, Brogan A, Walker AJ, Lewis T. Optimising laboratory monitoring of chronic conditions in primary care: a quality improvement framework. *BMJ Open Qual*. 2019;8(1):e000349. doi:10.1136/bmjoq-2018-000349
32. CPIC® guideline for tacrolimus and CYP3A5 [Internet]. Accessed May 4, 2022. https://cpicpgx.org/guidelines/guideline-for-tacrolimus-and-cyp3a5/
33. Pallet N, Etienne I, Buchler M, et al. Long-term clinical impact of adaptation of initial tacrolimus dosing to *CYP 3A5* genotype. *Am J Transplant*. 2016;16(9):2670-2675. doi:10.1111/ajt.13788
34. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *BMJ*. 2008;336(7653):1114-1117. doi:10.1136/bmj.39553.670231.25
35. Peyser B, Perry EP, Singh K, et al. Effects of delivering *SLCO1B1* pharmacogenetic information in randomized trial and observational settings. *Circ Genom Precis Med*. 2018;11(9):e002228. doi:10.1161/CIRCGEN.118.002228
36. GOV.UK. Criteria for appraising the viability, effectiveness and appropriateness of a screening programme [Internet]. Accessed May 4, 2022. https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme
37. Plumpton CO, Alfirevic A, Pirmohamed M, Hughes DA. Cost effectiveness analysis of HLA-B*58:01 genotyping prior to initiation of allopurinol for gout. *Rheumatology*. 2017;56(10):1729-1739. doi:10.1093/rheumatology/kex253
38. Chen P, Lin JJ, Lu CS, et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. *N Engl J Med*. 2011;364(12):1126-1133. doi:10.1056/NEJMoa1009717
39. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med*. 2011;364(12):1134-1143. doi:10.1056/NEJMoa1013297
40. Mushiroda T, Takahashi Y, Onuma T, et al. Association of HLA-A*31:01 screening with the incidence of carbamazepine-induced cutaneous adverse reactions in a Japanese population. *JAMA Neurol*. 2018;75(7):842-849. doi:10.1001/jamaneurol.2018.0278
41. Kheiri B, Abdalla A, Haykal T, et al. Meta-analysis of genotype-guided versus standard dosing of vitamin K antagonists. *Am J Cardiol*. 2018;121(7):879-887. doi:10.1016/j.amjcard.2017.12.023
42. Holtzman NA, Watson MS. Promoting safe and effective genetic testing in the United States. Final report of the Task Force on Genetic Testing. *J Child Fam Nurs*. 1999;2(5):388-390. doi:10.1093/clinchem/45.5.732
43. McDermott JH, Mahaveer A, James RA, et al. Rapid point-of-care genotyping to avoid aminoglycoside-induced ototoxicity in neonatal intensive care. *JAMA Pediatr*. 2022;176(5):486-492. doi:10.1001/jamapediatrics.2022.0187
44. Hughes DA. Economics of pharmacogenetic-guided treatments: underwhelming or overstated? *Clin Pharmacol Ther*. 2018;103(5):749-751. doi:10.1002/cpt.1030
45. Hughes DA, Vilar FJ, Ward CC, Alfirevic A, Park BK, Pirmohamed M. Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity. *Pharmacogenetics*. 2004;14(6):335-342. doi:10.1097/00008571-200406000-00002
46. Kimpton JE, Carey IM, Threapleton CJD, et al. Longitudinal exposure of English primary care patients to pharmacogenomic drugs: an analysis to inform design of pre-emptive pharmacogenomic testing. *Br J Clin Pharmacol*. 2019;85(12):2734-2746. doi:10.1111/bcp.14100
47. Klieber M, Oberacher H, Hofstaetter S, et al. CYP2C19 phenoconversion by routinely prescribed proton pump inhibitors omeprazole and esomeprazole: clinical implications for personalized medicine. *J Pharmacol Exp Ther*. 2015;354(3):426-430. doi:10.1124/jpet.115.225680
48. World Health Organization. Guide to G6PD deficiency rapid diagnostic testing to support *P. vivax* radical cure [Internet]. Geneva: World Health Organization; 2019. Accessed May 25, 2022. https://apps.who.int/iris/handle/10665/312082
49. Cooper-DeHoff RM, Niemi M, Ramsey LB, et al. The clinical pharmacogenetics implementation consortium guideline for *SLCO1B1*, *ABCG2*, and *CYP2C9* genotypes and statin-associated musculoskeletal symptoms. *Clin Pharma and Therapeutics*. 2022;111(5):1007-1021. doi:10.1002/cpt.2557
50. Using pharmacogenomic information in clinical practice—PRSB [Internet]. Accessed May 4, 2022. https://theprsb.org/projects/geneticsandmedicines/
51. Chen Z, Liew D, Kwan P. Effects of a HLA-B*15:02 screening policy on antiepileptic drug use and severe skin reactions. *Neurology*. 2014;83(22):2077-2084. doi:10.1212/WNL.0000000000001034

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