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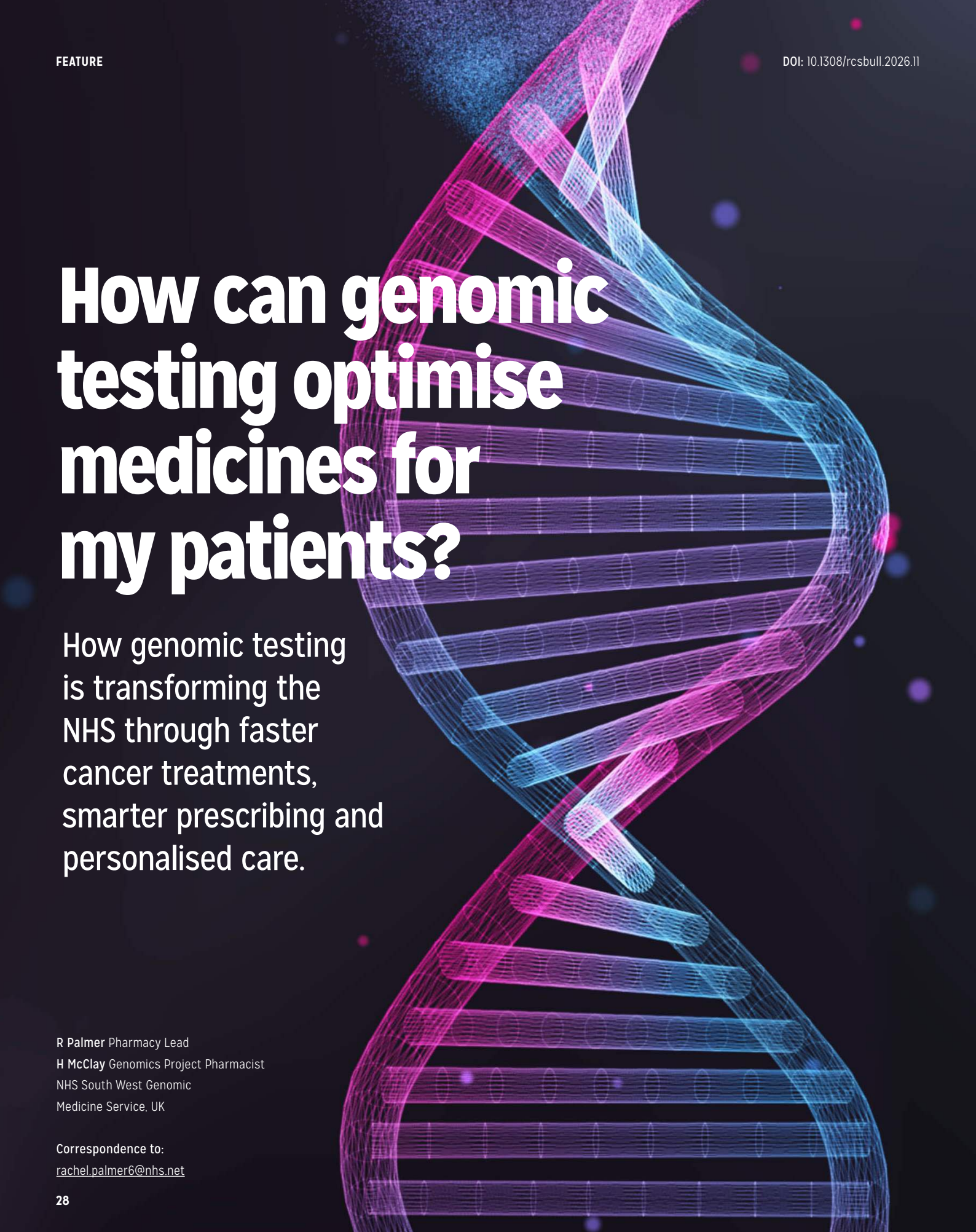
How can genomic testing optimise medicines for my patients?

How genomic testing is transforming the NHS through faster cancer treatments, smarter prescribing and personalised care.



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The NHS 10 Year Health Plan for England highlights genomics as a priority for improving how medicines are selected and used, with up to 50% of healthcare episodes predicted to involve genomics by 2035.[1] As testing expands, targeted therapies and pharmacogenomics will increasingly influence surgical pathways, helping us choose safer perioperative drugs, anticipate adverse reactions, and tailor adjuvant and neoadjuvant treatments. For surgeons, this means more effective care, fewer complications and better outcomes for our patients.

TARGETED THERAPIES IN CANCER

All cancer patients will receive comprehensive genomic profiling, with the aim of identifying a targetable variant for precision medicines. Circulating tumour DNA (ctDNA) testing has been mainstreamed in the NHS for non-small cell lung cancer in order to reduce the time from diagnosis to targeted treatment initiation. It has also been introduced successfully in breast cancer to enable access to elacestrant (a selective oestrogen receptor degrader) by identifying patients with emerging *ESR1* genetic variants, conferring resistance to traditional hormone therapies.[2] With the NHS 10 Year Plan, it is proposed that the use of ctDNA will be expanded, including as a means of monitoring treatment response and the emergence of treatment-resistant variants in solid tumours.[1]

PHARMACOGENOMICS

Pharmacogenomics studies how an individual's genomic make-up can influence how they respond to medicines, including treatment efficacy and adverse effects. The NHS 10 Year Plan describes how pharmacogenomic testing will be embedded into routine care at a population health level.[1] While pharmacogenomic testing is still at a relatively early stage in the NHS, there are several evidence-based examples of pharmacogenomic testing, supported by international guidance, that may affect surgical pathways in the future.

DPYD genotyping in solid tumours

Around 3–5% of the UK population carry variants in the *DPYD* gene, which predisposes them to life-threatening or even fatal toxicity with fluoropyrimidine chemotherapy (fluorouracil, capecitabine, tegafur).[3] Pharmacogenomic testing for *DPYD* variants has been embedded in NHS treatment pathways since 2021 in order to improve care by reducing adverse drug reactions.

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General anaesthesia

Pharmacogenomic testing can also play a future role in optimising general anaesthesia. Patients with variants in the *BCHE* gene are prone to prolonged neuromuscular blockade with mivacurium and succinylcholine owing to reduced metabolism, with the US Food and Drug Administration advising to avoid use in poor metabolisers.[4] Multiple genetic variants in *RYR1* and *CACNA1S* are categorised as diagnostic variants for malignant hyperthermia by the European Malignant Hyperthermia Group.[5] As these variants are rare, routine genotyping is not advocated but international guidance from the Clinical Pharmacogenetics Implementation Consortium advises that genotyping should be undertaken following a positive muscle biopsy for malignant hyperthermia.[6] If a relevant *RYR1* or *CACNA1S* variant is found, cascade testing should be implemented for family members.

Analgesia

The *CYP2D6* isoenzyme is responsible for metabolising around 20% of commonly prescribed medicines and has a significant impact on the metabolism of prodrugs tramadol and codeine to their active component, morphine. Around 7–10% of Caucasians are *CYP2D6* poor metabolisers,[7] resulting in inadequate analgesia with codeine or tramadol. Conversely, *CYP2D6* ultra-rapid metabolisers account for up to 6.5% of Caucasians and 29.0% of people of Ethiopian/African ancestry;[7] these groups are at increased risk of opioid toxicity at normal doses. The UK Medicines and Healthcare products Regulatory Agency (MHRA) advises that codeine should be avoided in those known to be *CYP2D6* ultra-rapid metabolisers owing to the risk of toxicity.[7]

Although most pharmacogenomic variants exert their effect via altering drug metabolism, genetic variants in human leucocyte antigen genes can predispose individuals to an increased risk of type B (idiosyncratic) adverse drug reactions. Carbamazepine, which may be utilised in the management of neuropathic pain, has been associated with an increased risk of Stevens–Johnson syndrome and toxic epidermal necrolysis in patients with *HLA-B1502* variants.[8] These variants are rare in European ancestry patients but are more common in Asian populations. The MHRA advises that clinicians should

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consider *HLA-B1502* genotyping for Han Chinese, Hong Kong Chinese and Thai ancestry patients prior to commencing carbamazepine.[8]

Clopidogrel

Clopidogrel is a prodrug, metabolised to its active form predominantly by the *CYP2C19* isoenzyme. Around a quarter to a third of the UK population display at least one loss-of-function *CYP2C19* genetic variant and are less able to activate clopidogrel. This increases to 57% in patients of Bangladeshi or Pakistani ancestry.[9] While a strong evidence base underpins the use of *CYP2C19* genotyping in stroke and cardiovascular indications to reduce repeat ischaemic events, further data are required to support the role of genotyping for peripheral artery disease (PAD) patients due to receive clopidogrel.[10] The ongoing GENPAD clinical trial has randomised 2,276 PAD patients to conventional clopidogrel or *CYP2C19* genotype-guided antithrombotic therapy.[11] The trial will assess a composite primary outcome of myocardial infarction, ischaemic stroke, cardiovascular death, acute/chronic limb ischaemia, PAD interventions or death. Bleeding complications are also to be analysed.

Anti-infective agents

Metagenomic testing (the testing of all genetic material in a sample) has been shown to identify pathogens more rapidly than traditional microbiology culture.[12] It also has the potential to identify genetic variants conferring resistance to anti-infective agents. The use of host genomic profiling can also identify high-risk patients, allowing stratification of prophylaxis and treatment. The use of metagenomics in severe respiratory infection is currently being evaluated via an NHS Genomic Network of Excellence.

Mitochondrial variants in the *MT-RNR1* gene can predispose patients to sudden onset severe hearing loss and vestibular disorders with aminoglycoside antibiotics.[13] Pre-emptive testing is available via the NHS Genomic Medicine Service for patients predisposed to Gram-negative infection as a result of an underlying medical condition (e.g. cystic fibrosis) or where hearing loss has already occurred in the context of aminoglycoside exposure. Pharmacogenomics can also help optimise antifungal therapy. Voriconazole (an azole antifungal agent) is metabolised by *CYP2C19*, with international pharmacogenomic guidance advising consideration of alternative therapy for patients who are ultra-rapid or poor *CYP2C19* metabolisers owing to the risk of subtherapeutic or excessive plasma levels respectively.[14]

HOW MAY WE IMPLEMENT PHARMACOGENOMIC TESTING IN FUTURE?

At present, pharmacogenomic testing is predominantly undertaken reactively once an individual is about to be prescribed a specific medicine. As a relatively small number of pharmacogenes affect the metabolism of multiple medicines, the testing of a panel of the most common pharmacogenes (with the ability to store and reuse the results for future prescribing) offers a more efficient solution. This may be employed pre-emptively at a certain age or at the onset of a long-term medical condition. However, the advantages of this approach will only be fully realised with the integration of genomic test results into electronic patient records, and the awareness and ability of healthcare professionals across sectors to access and competently action pharmacogenomic results.

The PROGRESS study is currently investigating the feasibility of panel based pharmacogenomic testing in primary care and is assessing the health economic benefits in the NHS system.[15] Importantly, as part of this study, pharmacogenomic results are presented as prescribing advice, which can be surfaced by clinical decision support systems in general practice, rather than a genetics report containing a diplotype or phenotype.

The role of the NHS Genomic Medicine Service is set to expand substantially and pharmacogenomic testing will be embedded into routine practice at a population level. It is therefore key that all healthcare professions are armed with the necessary awareness of genomics, knowledge and competence to advance patient care.

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