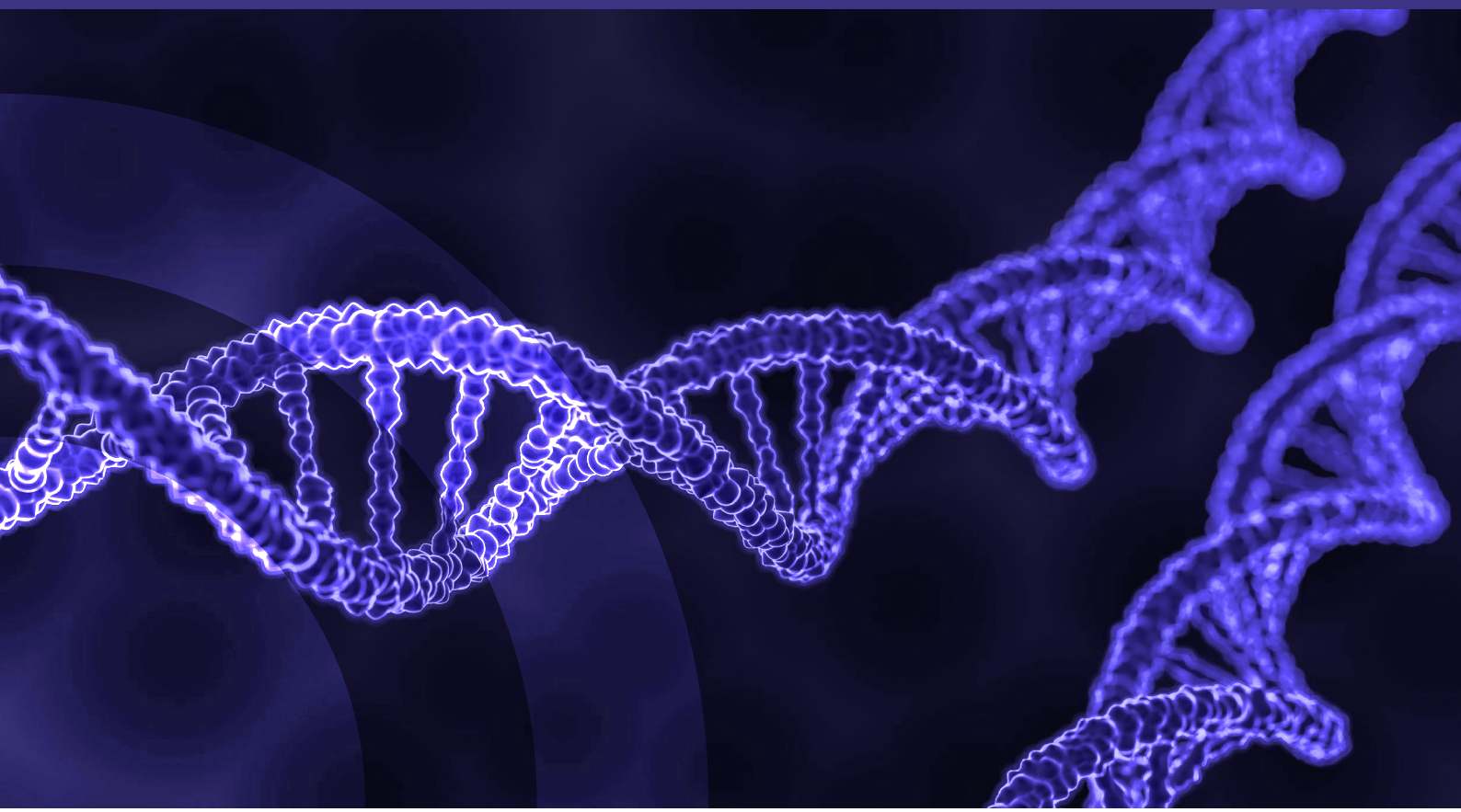
NHS RACE & HEALTH OBSERVATORY

GENETIC TESTING TO REDUCE SIDE EFFECTS FROM CHEMOTHERAPY DRUGS IN THE NHS

A LAY SUMMARY



July 2024

BACKGROUND

***Pharmacogenomics* is the study of how people's genes affect their response to drugs. This can help to determine whether the drug will work well, and how safe it is. It can help to identify how a patient's genes might impact how a drug interacts with their body.**

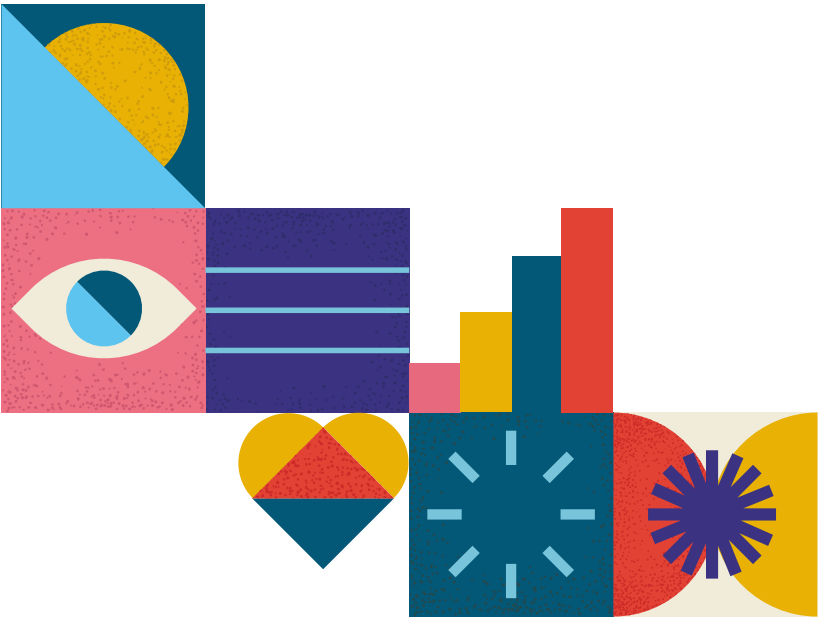
However, most genetic tests used in the NHS and worldwide focus on genes found in White European populations. This poses a problem because these tests might not be as effective for people of Black, Asian, and other ethnic minority groups. This is especially concerning in precision medicine, where treatments are tailored to an individual's genetic profile.

A specific example of this is DPYD genetic testing. DPYD is a gene which helps to control how much dihydropyrimidine dehydrogenase

(DPD) is produced in the body. DPD is an enzyme that breaks down certain anticancer drugs called fluoropyrimidines. These drugs have a narrow safety window between the minimum effective dose and maximum tolerated dose. A deficiency of the DPD enzyme can lead to the inadequate breakdown of the drug resulting in increased drug exposure, which can lead to serious side effects. Testing for DPD deficiency can help doctors adjust the drug dosage to avoid harm.

DPD deficiency can be detected in 39–61% of patients with severe fluoropyrimidine-related side effects.[1] Where this enzyme deficiency is identified, a clinician can prescribe a lower the dose, or offer a different type of chemotherapy drug, therefore reducing the risk of serious or life-threatening side effects.

In October 2020, the Medicines Healthcare products Regulatory Agency (MHRA), the UK regulator recommended that clinicians carry out DPD testing before prescribing fluoropyrimidine drugs. In November 2020, the NHS implemented DYPD genetic testing as a pre-treatment screening test prior to using fluoropyrimidine based therapies. This is one of the first pharmacogenomic tests to be applied nationally in the UK. However, since these tests are based on genes identified in White European populations, they may not be as effective for Black and ethnic minority patients, potentially increasing health inequalities.



THE PROJECT

The NHS Race and Health Observatory, in partnership with the Wolfson Centre for Personalised Medicine at the University of Liverpool, is working on a project to address these inequalities. The aim is to identify new genetic changes (variants) in the DYPD gene that are relevant to a broader range of ethnic groups served by the NHS. We know that testing for variants in the DPYD gene focuses on four variants found primarily in people with White European ancestry and that this has the potential to worsen health and race inequalities in ethnically diverse societies. Furthermore, it does not help other countries where the population is predominantly of non-European ancestry, as DPYD genetic testing will not be implemented due to lack of evidence. It is crucial that all global populations benefit equally from this important genetic test.

The study team includes Dr Tsun Ho Chan and Dr J. Eunice Zhang, with leadership from Professor Sir Munir Pirmohamed.

FOUR MAIN GOALS OF THE PROJECT

1. Review existing studies on DYPD genetic variants.
2. Assess these variants using computer models.
3. Sequence the DYPD gene in diverse populations.
4. Advocate for expanding the number of tested variants in the DYPD gene.

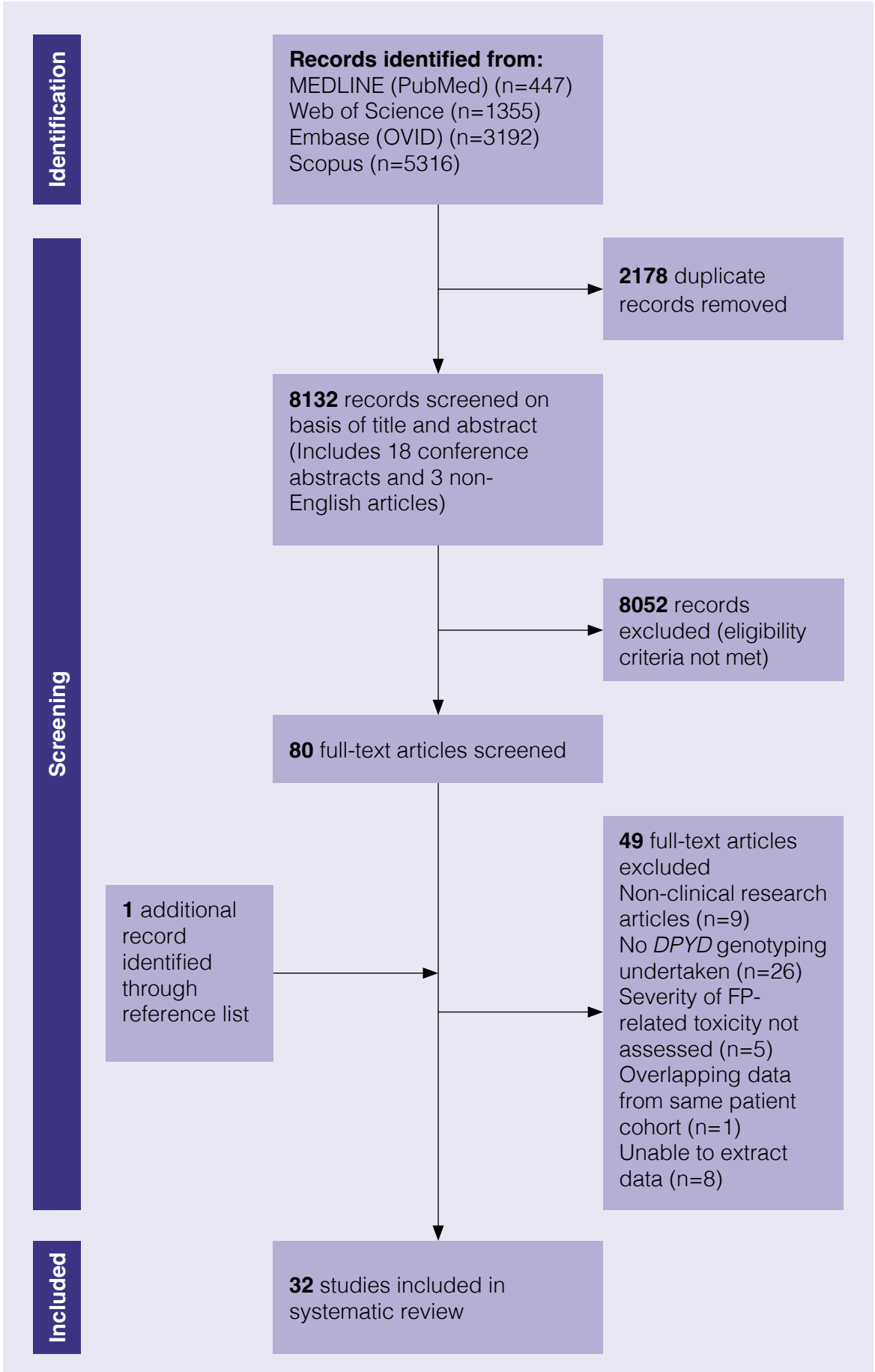
SYSTEMATIC REVIEW

The first part of the project involved a review of current research to find DPYD gene variants linked to severe side effects from fluoropyrimidine based drugs in black and ethnic minority populations. The review focused on studies up to April 2023, looking at genetic research on patients who had severe reactions to these drugs. The results of this study can be found in the British Journal of Cancer.

METHODS

The aim was to identify variants of the DPYD gene that could be added to routine testing, to increase the chance of identifying dangerous deficiencies in patients who are not of White European ancestry. Researchers focused on clinical studies and case reports that looked at patients from non-European backgrounds who experienced severe side effects from chemotherapy containing fluoropyrimidines. They selected and assessed studies that met their criteria for quality. Figure 1 shows a flow diagram of study selection. In total 8132 articles were screened on the basis of their title and abstract.

Figure 1. Flow diagram of study selection



FINDINGS

The review found 32 relevant studies, published between 1998 and 2022. The researchers found that 53 DPYD variants were evaluated in patients from 12 countries from 5 ethnic groups: African American, East Asian, Latin American, Middle Eastern, and South Asian. The review found several DPYD gene variants in non-European individuals. While the UK currently tests for four DPYD variants, mainly found in White Europeans, three of these were also found in non-European populations. However, more variants need to be identified to improve testing accuracy for all ethnic groups.

The study team found strong evidence for a specific genetic variant, **c.557A>G variant**, which is found in individuals of African ancestry, but is not currently included in the UK DYPD genetic testing.

The review highlighted a lack of data on certain populations, such as those from the Middle East and Latin America, emphasising the need for more research. It also noted that understanding the full range of harmful mutations in the DPYD gene requires further patient identification and gene sequencing.

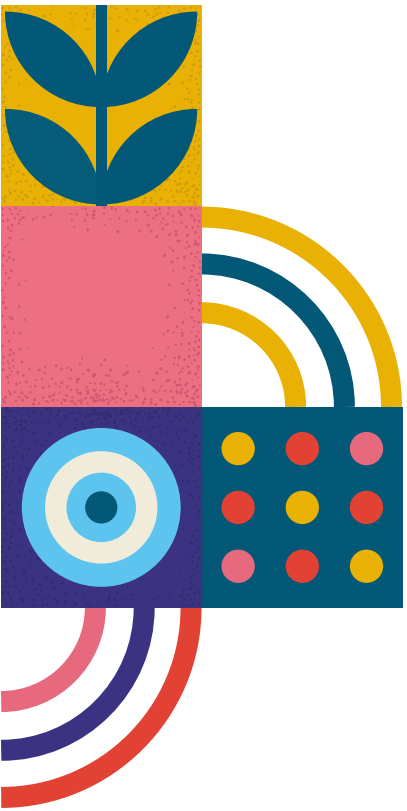
Previous studies have shown that people with DPD enzyme deficiencies are at higher risk for severe toxicity from standard doses of fluoropyrimidines. Testing before treatment and adjusting doses accordingly can significantly reduce these risks and is also cost-effective. For example, a UK-based study of an extended DPYD genetic panel showed that genotyping could lead to a saving of £78,000 per patient over a lifetime.[2]

LIMITATIONS

The review relied on observational studies, which might not cover all relevant cases. Some important genetic variants might be missed because they were not reported or tested. More comprehensive patient sequencing is needed to fully understand the DPYD gene's variations.

CONCLUSION

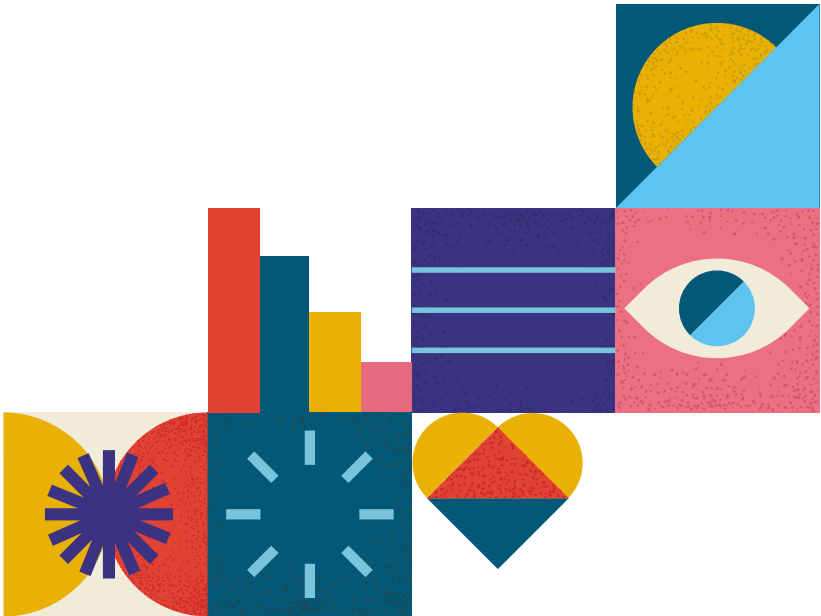
This systematic review has focused on non-European patients and has identified several variants in the *DPYD* gene which have been associated with severe toxicity after treatment with fluoropyrimidine based anti-cancer drugs. The UK is multi-cultural and ethnically diverse society but we only test for 4 variants which have been identified from studies undertaken in European populations. This work shows that 3 of these 4 variants are also important in South Asian, East Asian and Middle Eastern people. **The study team and the NHS Race and Health Observatory have recommended to extend DPYD genetic testing in the UK NHS to include the c.557A>G variant which has been identified in individuals of African ancestry. This decision is currently under review. If successful, testing for the variant will be included in the National Genomic Test Directory.**



REFERENCES

1. van Kuilenburg AB. *Dihydropyrimidine dehydrogenase and the efficacy and toxicity of 5-fluorouracil.* Eur J Cancer. 2004;40:939–50.

2. Koleva-Kolarova R, Vellekoop H, Huygens S, Versteegh M, Mölken MR, Szilberhorn L, et al. *Budget impact and transferability of cost-effectiveness of DPYD testing in metastatic breast cancer in three health systems.* Per Med. 2023;20:357–74.



nhsrho.org

@nhs_rho