Technoleg Iechyd Cymru
Health Technology Wales

# Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

- Determine the quantity of evidence available for a technology of interest.
- Identify any gaps in the evidence.
- Inform decisions on topics that warrant fuller assessment by Health Technology Wales (HTW).

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| **Topic exploration report number:** | TER465 |
| **Topic:** | Pre-emptive pharmacogenetic (PGx) testing using a multiple gene panel to guide treatment and reduce adverse drug reactions |
| **Summary of findings:** | Pharmacogenetics (also referred to as pharmacogenomics; PGx) is the study of how a person's genes affect their response to medications. Differences in genes may result in a particular medicine being effective for some people, but not others. Equally, it may be the reason that some people experience side effects (or adverse reactions) to a medicine, whilst others do not. The benefit of PGx testing before starting medications has been well documented for several single gene–drug pairs. This topic exploration report focuses on pre-emptive PGx testing using a multiple gene panel to guide treatment and reduce adverse drug reactions.<br>Five systematic reviews in specific populations were identified; however, there are significant limitations in the body of evidence and only one focussed on adverse drug reactions. The latter reported that prospective screening may reduce severe hypersensitivity reactions to abacavir in patients positive for HIV-type 1. Some clinical/efficacy benefits were reported in depression, mood disorders, anxiety, schizophrenia and metastatic colorectal cancer.<br>HTW researchers identified two primary studies. An open-label, multicentre, controlled, cluster-randomised crossover implementation study in Europe (including UK) reported that genotype-guided treatment using a 12-gene PGx panel significantly reduced the incidence of clinically relevant adverse drug reactions. Another study showed that the use of PGx testing before hip and knee arthroplasty may lower pain levels.<br>There is limited evidence on the clinical utility of pre-emptive testing using a PGx panel of multiple gene-drug pairs in order to guide treatment and reduce adverse drug reactions. Furthermore, it is unclear how different PGX panel tests compare.<br>There is limited economic evidence on the use of PGx testing using a multiple gene panel. |

## Introduction and aims

Pharmacogenetics (also referred to as pharmacogenomics; PGx) is the study of how a person's genes affect their response to medications. It is a branch of precision (or personalised) medicine, which allows clinicians to select an individualised treatment that is optimised for a person based on their genetic makeup. Differences in genes may result in a particular medicine being effective for some people, but not others. Equally, it may be the reason that some people experience side effects (or adverse reactions) to a medicine, whilst others do not. The test is usually performed on a sample of blood, saliva or cells from a cheek swab, which in some cases may be collected using a home test kit. PGx testing is different to genetic testing. The latter is carried out to help diagnose conditions or identify risk for developing conditions.

The benefit of PGx testing before starting medications has been well documented for several single gene–drug pairs. However, there is a need to consider the clinical utility (benefit, risk and value in medical decision making) of pre-emptive testing using a PGx panel of multiple gene-drug pairs in order to guide treatment and reduce adverse drug reactions.

Health Technology Wales researchers searched for evidence on the clinical and cost effectiveness of pre-emptive testing using a PGx panel to guide treatment and reduce adverse drug reactions.

## Evidence overview

HTW researchers identified health technology evaluations and guidance on genetic testing (see literature search results); however, there is a lack of assessments and guidance on pre-emptive testing using a PGx panel to guide treatment and reduce adverse drug reactions.

Five systematic reviews in specific populations were identified, with one focussing on adverse drug reactions. Two individual studies are also included, one assessing a 12-gene PGx panel to prevent adverse drug reactions and another on the use of PGx testing before hip and knee arthroplasty to customise postoperative pain medication (see below).

There was limited economic evidence on the use of PGx testing using a multiple gene panel.

**Evidence reviews**

Three systematic reviews have been carried out on PGx testing in depression (Aboelbaha et al. 2021; Fabbri et al. 2018; Rosenblat et al. 2017). Minor clinical benefits were reported; however, there is a lack of evidence on safety outcomes. Fabbri et al. noted that only 9 of the ~40 commercial PGx tests available estimated potential clinical benefit. Health Quality Ontario carried out a systematic review of Assurex GeneSight-guided care compared to standard care in people with mood disorders, anxiety, or schizophrenia (Health Quality Ontario 2017). Improvements were reported in some patient outcomes, but not others. Furthermore, confidence in these findings was deemed low because of significant limitations in the body of evidence.

Lin et al. (2011) systematically reviewed EGFR-related PGx testing of molecular targets downstream to KRAS in the treatment of metastatic colorectal cancer. The evidence was considered most promising for BRAF mutation as a negative predictor of response to EGFR monoclonal antibodies, and was reportedly most robust for people with chemorefractory metastatic disease receiving cetuximab in combination chemotherapy. The authors note that this was based on low GRADE retrospective observational evidence.

**Individual studies**

Swen et al. (2023) assessed a 12-gene PGx panel to prevent adverse drug reactions in an open-label, multicentre, controlled, cluster-randomised crossover implementation study in Europe (including UK). Adults receiving a first prescription for a drug clinically recommended in the guidelines of the Dutch Pharmacogenetics Working Group (DPWG) as part of standard care were included. Participants were genotyped for 50 germline variants in 12 genes. Those with a drug–gene interaction test result for which the DPWG recommended a change to standard care (actionable variant) were treated according to DPWG recommendations (genotype-guided group; n=3,342), whilst the control group received standard care (n=3,602). A total of 449 (6·5%) participants carried no actionable variants and 6,495 (93·5%) participants carried at least one actionable variant. The most common index drug was atorvastatin (n=716), followed by clopidogrel (n=619), and tacrolimus (n=472).

The primary outcome was the occurrence of clinically relevant adverse drug reactions within the 12-week follow-up period. The authors used a gatekeeping analysis, in which outcomes in participants with an actionable drug–gene interaction in the genotype-guided group were compared to the control group, and analysis of all study participants was only carried out if this difference was statistically significant. In the first gatekeeping analysis, 195 (11·1%) of 1,753 participants with actionable variants did not complete the 12-week follow-up. In patients with an actionable test result for the index drug (n=1,558), a clinically relevant adverse drug reaction occurred in 152 (21·0%) of 725 patients in the genotype-guided group and 231 (27·7%) of 833 participants in the control group (odds ratio [OR] 0·70 [95% confidence interval (CI) 0·54 to 0·91]; p=0·0075). For the analysis of all participants, the incidence was 628 (21·5%) of 2,923 participants in the genotype-guided group and 934 (28·6%) of 3,270 participants in the control group (OR 0·70 [95% CI 0·61 to 0·79]; p <0·0001). However, it is notable that no significant difference was found when only considering UK data.

A prospective randomised study by Hamilton et al. (2022) assessed the use of a 16-gene PGx panel before hip and knee arthroplasty to customise postoperative pain medication. Participants recorded their pain level on a numeric scale and all medications were taken daily for the first 10 days post-operatively. Medication was converted to milligram morphine equivalents (MMEs). Genetic variations to medications occurred in 24 (22.4%) of the 107 participants. The mean 10-day MME for the customised group with variants was 86.7mg as compared to 162.7mg in the control group with variants (p=0.126). A lower 10-day average pain was reported for the customised group with variants as compared to the control group with variants (3.08 vs 4.24; p=0.026).

**Economic evidence**

Plöthner et al. (2016) carried out a systematic review of the cost-effectiveness and cost-utility of PGx tests. A total of 27 studies were included, however the search did not exclude single gene-drug pair testing. The systematic review considered PGx testing in numerous specific therapeutic areas, with a large number in oncology. In most studies, a PGx-guided treatment was reportedly cost-effective or would lead to cost savings. The authors note that the cost-effectiveness depends on various factors, including sensitivity and specificity of test procedures, prevalence of biomarkers, test costs, threshold value, prevalence of adverse drug reactions, response rate of therapy, and the perspective of the study. Differences in cost-effectiveness were found even within the same indications.

## Areas of uncertainty

The benefit of PGx testing before starting medications has been well documented for several single gene–drug pairs. However, there is limited evidence on the clinical utility of pre-emptive PGx testing using a panel of multiple gene-drug pairs in order to guide treatment.

There is limited evidence specifically focussing on PGx panel testing to reduce adverse drug reactions. The study by Swen et al. (2023) does not report specifically on important clinical outcomes such as hospitalisations and mortality, although the clinically relevant adverse drug reactions reported would incorporate these.

It is unclear how different PGX panel tests compare.

There is limited economic evidence on the use of PGx testing using a multiple gene panel.

## Literature search results

### Health technology assessments and guidance

EUnetHTA. (2018). Added value of using gene-expression signature for adjuvant chemotherapy decisions in early breast cancer. EUnetHTA OTC04. European Network for Health Technology Assessment. Available at: https://www.eunethta.eu/final-assessment-report-on-mammaprint-added-value-of-using-the-gene-expression-signature-test-mammaprint-for-adjuvant-chemotherapy-decision-making-in-early-breast-cancer/ [Accessed 25 April 2023].

HIQA. (2023). A rapid HTA of gene expression profiling tests for guiding the use of adjuvant chemotherapy in early-stage invasive breast cancer. Health Information and Quality Authority. Available at: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/rapid-hta-gene-expression-profiling-tests [Accessed 25 April 2023].

NICE. (2023). Genedrive MT-RNR1 ID Kit for detecting a genetic variant to guide antibiotic use and prevent hearing loss in babies: early value assessment. Health technology evaluation (HTE6). National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/hte6 [Accessed 25 April 2023].

NICE. (2018). Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. Diagnostics guidance (DG34). National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/dg34 [Accessed 25 April 2023].

SHTG. (2020). Pre-treatment DPYD genetic testing for patients who are prescribed chemotherapy involving fluoropyrimidines. SHTG assessment number 04. Scottish Health Technologies Group. Available at: https://shtg.scot/our-advice/pre-treatment-dpyd-genetic-testing-for-patients-who-are-prescribed-chemotherapy-involving-fluoropyrimidines/ [Accessed 25 April 2023].

SHTG. (2022). Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. SHTG recommendation project scope. Scottish Health Technologies Group. Available at: https://shtg.scot/our-advice/tumour-profiling-tests-to-guide-chemotherapy-decisions-in-early-breast-cancer/ [Accessed 25 April 2023].
*SHTG recommendation expected October 2023.*

### Evidence reviews and economic evaluations

Aboelbaha S, Zolezzi M, Elewa H. (2021). Effect of pharmacogenetic-based decision support tools in improving depression outcomes: A systematic review. Neuropsychiatric Disease and Treatment. 17: 2397-2419. doi: https://doi.org/10.2147/ndt.s312966.

Fabbri C, Zohar J, Serretti A. (2018). Pharmacogenetic tests to guide drug treatment in depression: Comparison of the available testing kits and clinical trials. Progress in Neuropsychopharmacology and Biological Psychiatry. 86: 36-44. doi: https://doi.org/10.1016/j.pnpbp.2018.05.007.

Health Quality Ontario. (2017). Pharmacogenomic Testing for Psychotropic Medication Selection: A Systematic Review of the Assurex GeneSight Psychotropic Test. Ontario Health Technology Assessment Series. 17(4): 1-39. Available at: http://www.ksrevidence.com/article/KSRA29688 [accessed 25 April 2023].

Lin JS, Webber EM, Senger CA, et al. (2011). Systematic review of pharmacogenetic testing for predicting clinical benefit to anti-EGFR therapy in metastatic colorectal cancer. Am J Cancer Res. 1(5): 650-62. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3139487/ [Accessed 25 April 2023].

Plöthner M, Ribbentrop D, Hartman JP and Frank M. (2016). Cost-effectiveness of pharmacogenomic and pharmacogenetic test-guided personalized therapies: A systematic review of the approved active substances for personalized medicine in Germany. Advances in Therapy. 33(9): 1461-80. doi: https://doi.org/10.1007/s12325-016-0376-8.

Rosenblat JD, Lee Y, McIntyre RS. (2017). Does pharmacogenomic testing improve clinical outcomes for major depressive disorder? A systematic review of clinical trials and cost-effectiveness studies. Journal of Clinical Psychiatry. 78(6): 720-9. doi: https://doi.org/10.4088/jcp.15r10583.

### Individual studies

Hamilton WG, Gargiulo JM, Reynolds TR and Parks NL. (2022). Prospective randomized study using pharmacogenetics to customize postoperative pain medication following hip and knee arthroplasty. Journal of Arthroplasty. 37(6S): S76-81. doi: https://doi.org/10.1016/j.arth.2022.02.037.

Swen JJ, van der Wouden CH, Manson LE, et al. (2023). Ubiquitous Pharmacogenomics Consortium. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. Lancet. 401(10374): 347-356. doi: https://doi.org/10.1016/s0140-6736(22)01841-4.

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| **Date of search:** | April 2023 |
| **Concepts used:** | Adverse drug reactions; clinical utility; genotype; implementation; Mantara; panel; PGx; pharmacogenetic; pre-emptive. |

## Proposed research question and evidence selection criteria (if selected)

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| **Proposed research question** | **Is it clinically and cost effective to perform pre-emptive PGx testing using a multiple gene panel to guide treatment and reduce adverse drug reactions?** |

| | Included | Excluded |
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| **Population** | People who may benefit from pre-emptive PGx testing using a multiple gene panel to guide treatment and reduce adverse drug reactions (i.e. not restricted to a specific treatment and/or condition) | Previous genetic testing (direct-to-consumer or clinical) for a gene relevant to the index drug, a planned duration of treatment less than seven consecutive days, and severe renal or liver insufficiency. |
| **Intervention** | Pre-emptive genetic testing using a PGx panel to guide treatment | Testing single gene drug pairs<br>Genetic profiling |
| **Comparison/ comparators** | Standard care without pre-emptive genetic testing | |
| **Outcomes** | Incidence of causal and clinically relevant adverse drug reactions reported for the index drug within the 12-week follow-up period.<br>Treatment switches<br>Quality of life<br>Costs | |
| **Study design** | Any. Ideally systematic reviews/RCTs. Economic studies. | |