How can Pharmacogenomics Improve Symptom Management for Palliative and Supportive Care? A Scoping Review

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Abstract

Context: Pharmacogenomics (PGx) is an area of expanding research, and could indicate whether an individual is likely to benefit from a symptom control medication. Palliative supportive care (PSC) could be an area that benefits from PGx, however, little is known about the current evidence base for this.

Objective: To determine how pharmacogenomics (PGx) can be applied in PSC, whether there is any evidence of benefit, and to understand the extent and type of evidence that supports the use of PGx in PSC.

Methods: A search of 6 databases up to July 2024. Reference snowballing from review articles and screened papers was used to identify any missed articles.

Results: 11 articles were reviewed. 550 patients had a PGx test across 8 / 11 studies. Up to half of the patients had an actionable PGx result, and in one study there were 4.6 drug –gene interactions per patient. Implementation of PGx was found to be feasible. Clinician adherence to advice given was under reported. No studies reported health economics analysis, or was designed to definitively answer whether PGx was better than standard care.

Conclusions: It is both feasible and acceptable to conduct PGx testing in a supportive and palliative care setting. Many supportive care medications are amenable to PGx. Clinician adherence to recommendations is variable and there is no clear evidence that PGx enhances palliative/supportive care patient outcomes. Prospective, clinical trials are needed to establish whether PGx can improve symptom management for people receiving palliative and supportive care.

Key Message: This review highlights that pharmacogenomics is a promising area of medicine that is relevant to symptom management in palliative and supportive care, despite an absence of UK studies in this area.

Keywords: Genetic Medicine, Genomics, Palliative Care, Personalised Medicine, Pharmacogenomics, Supportive Care.

- **What is already known on this topic** – P*harmacogenomics is a potential tool in the armoury of personalised medicine, where information about drug-gene interactions can be used to guide individualised prescribing practice.*
- **What this study adds** – *Many of the medications used in palliative and supportive care may be susceptible to drug-gene interactions, which may determine how effective those medications are at achieving symptom control. Testing people for these genetic variations appears to be both feasible and acceptable in a palliative care context, although no such studies have taken place in the UK*

- **How this study might affect research, practice or policy** – *Prospective, clinical trials are needed to establish whether PGx can improve symptom management for people receiving palliative and supportive care.*

1. Introduction

Two decades since the publication of the first fully sequenced human genome, we live in an age of personalised medicine. (1) Treatment choices, shaped by an individuals' genetic profile, are at the forefront of many medical specialties, particularly in oncology. (2) The concept of "medicines optimisation" has also received increasing attention over the past two decades, with focus both on initiating the correct medicine for a patient at the first time of asking, and in stopping or deprescribing inappropriate or harmful medications. (3,4) Pharmacogenomics (PGx) has the potential to further personalise medicines optimisation.

Variation in gene expression, particularly in the cytochrome P450 family of genes, means that an individual will either produce an enzyme that is likely to poorly metabolise (PM), intermediately metabolise (IM), normally metabolise (NM) or ultra metabolise (UM) various medications. It is possible to perform a genetic analysis test on an individual patient and then use the result to quantify PM/IM/NM/UM status. This information can be used to review existing prescriptions, and to guide future prescribing intentions for a wide range of medications against published expert advice. (5) Single-gene, or a multiple-gene tests (also called a panel test) are available, the use of which depends on protocol and/or clinical choice.

Proponents of PGx argue that it should be in wider use, whilst acknowledging that there are still barriers to implementation. (6) One of those barriers is the lack of evidence for PGx outside of the specialties where it has been most studied. The largest evidence bases exist for medicines prescribed in cardiology, stroke, psychiatry and oncology. (5) This evidence originates from trials conducted mostly outside of the United Kingdom, with health economic impact calculations that are less relevant to the way NHS finances are structured.

Whilst medicines optimisation, particularly around the use of opioids, is recognised as an important component of supportive care and palliative care (7), little attention has been given to the role that pharmacogenomics might play in achieving the aims of supportive care, namely the right treatment at the right time. (8-10) As an area known to have a paucity of published research, a scoping review was undertaken to understand how research relevant to this population is conducted and to identify knowledge gaps relevant to the research question. (11,12)

Scoping Review question

The research question was: How can pharmacogenomics improve symptom management and supportive care?

Secondary questions were:-

(a) What drug-gene interactions are particularly relevant to supportive and palliative care?

(b) What implementation models for PGx have been studied with the intent to improve symptom management in supportive and palliative care?

(c) What is the extent and type of evidence in relation to the use of pharmacogenomic testing (PGx) in supportive and palliative care in cancer, specifically with reference to improved pain control?

We specifically chose to perform a scoping review rather than a systematic review as we are looking to identify gaps in the research literature and generate new research questions, relevant to this field.

2. Methods

This review was undertaken in line with the Joanne Briggs international (JBI) guidance on scoping reviews. (12) Findings are reported in line with Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-Scr) checklist. (11) This review was conducted in accordance with an *a priori* protocol. (13) Given the heterogenicity of the studies identified a narrative synthesis was also undertaken to integrate findings. A preliminary synthesis was conducted, exploring the relationships within and between the studies, which was refined over the course of the review, as per the approach described by Popay. (14)

2.1 Identification and selection of relevant studies

2.1.2 Search strategy

A search of 6 databases was conducted (namely Ovid Embase, Medline, Ovid Emcare, CINAHL, ADEM and PsycInfo), up to July 2024 using the key words above, and the phrase “test” or “pilot” or “implementation”, to restrict results to primary research, rather than reviews or meta-analyses. [Appendix 1 - example search on Ovid Medline] Reference snowballing from review articles was used and papers from the above search were screened to identify any missed articles.

The authors selected from this generated list those results that are publications that met inclusion criteria (i.e. a report of primary evidence of either use of a PGx test in a supportive or palliative care setting, or estimation of the prevalence of medicines in use in a supportive or palliative care setting that would be susceptible to a PGx test) and included them for data extraction and analysis. We also noted any review article, text or opinion piece for the purpose of identification of any further pieces of primary research and for background context. We conducted a scrutiny of reference lists of all included sources of evidence, plus background context articles to generate any additional relevant research publications - “reference snowballing”.

We restricted our search to studies published in English, as most PGx studies are published in this language. The above search strategy was aimed to locate only studies published in peer reviewed journals and we chose to exclude conference abstracts as they contain insufficient detail for our purpose.

2.2.2. Inclusion criteria

Inclusion criteria are outlined using the PCC - Patient / Concept / Context format (see Table 1).

Table 1: Inclusion Criteria

	Inclusion	**Exclusion**
Participants	Adult patients under the care of a supportive care / palliative care service (including oncology services)	Participants not known to have either cancer, or a life-limiting condition
Concept	The use of, discussion of, or evaluation of potential use cases for pharmacogenomic testing with the intent to improve symptom management in supportive and palliative care	Pharmacogenomic testing not concerned with symptom management e.g. choice of chemotherapy agent
Context	Research performed in either outpatient or in-patient setting where supportive care / palliative care services are either integrated with primary attending team (e.g. oncology) or in charge of the clinical space.	Non clinical settings
Type of Sources	Experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, before and after studies. analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies. descriptive observational study designs including case series, individual case reports and descriptive cross-sectional studies. descriptive observational study designs including case series, individual case reports and descriptive cross-sectional studies	Systematic reviews, text and opinion papers. Grey Literature

2.2.3. Source of evidence selection

Following the search, all identified citations were collated and uploaded into a spreadsheet (Excel®) and duplicates removed. (15) Titles and abstracts were then screened independently by two reviewers (CB and MP) for assessment against the inclusion criteria for the review. Potentially relevant sources were retrieved, and the full text of these selected citations were assessed in detail against the inclusion criteria independently by the reviewers. Reasons for exclusion of sources of evidence at full text that do not meet the inclusion criteria were recorded. Any disagreements that arose between reviewers at each stage of the selection process were resolved through discussion.

2.2.4. Data extraction

We extracted data from the final list of publications as follows: year of study, number of PGx tests carried out, medicines class(es) tested, patient group selection, patient characteristics (sex and age), number of pharmacogenes tested, average number of drug-gene interactions (DGI), how often actionable PGx results influenced the prescribing practice of the medical team. For those studies conducted in a PICO format (16) we extracted further details for each PICO category, plus summary of outcomes reported, and general review notes. We extracted data on the exact type of pharmacogene tested where explicitly mentioned. Finally, we conducted an extraction of themes relevant to our primary research question and sub-questions as a narrative summary.

3. Results

The results of the search and the study inclusion process are presented in a PRISMA flow diagram. [Figure 1]. 11 articles were analysed. 1 article which include both paediatric and young adult patients was included as a minor deviation from our strategy, as both reviewers felt the article contained generalisable knowledge to adult palliative care settings. (17)

3.1. Characteristics of included studies

The selected characteristics and results shown in Table 2. These items were chosen after a consulting a list of key data extraction items to report derived from a non-setting specific PGx systematic review. (18)

Reference	Study focus (medicine) and / or patient population	Type of study	N of PGx tested	N (%) female of PGx tested	Mean age in years of PGx tested	Number pharmacogenes tested	average DGI per pt / % proportion of pts with actionable result	% of actionable results acted on by medics
Bull et al (2022)	Supportive medications in palliative care / palliative patients with chronic pain requiring daily morphine at ≥20 mg or equivalent for ≥1 week, and the chronic use of ≥4 nonopioid medications.	Prospective - single-arm feasibility trial	100	54	65	14	4.6 (SD 3.5)	NR
Mosley et al (2023)	Supportive medications in cancer / oncology patients	Prospective - randomised (non blinded) clinical trial	38	45	59	1	30%	18%
Patel et al (2021-a)	Supportive medications in cancer (Opioid specific) /oncology patients with uncontrolled pain at baseline	Prospective - single-arm interventional pilot trial	75	59	61	9	NR	NR
Philip et al (2023)	Supportive medications in cancer care (Opioid specific) / oncology patients	Prospective feasibility study	NR	NA	NA	NA	NA	NA
Vella-Brincat et al (2012)	Supportive medications in palliative care (Cyclizine specific) / general oncology patients	Prospective feasibility study	10	50	63	1	50%	NA
Wong et al (2023)	Supportive medications in cancer care (Opioid specific) / adult patients with incurable advanced cancer	Prospective - longitudinal study	54	44	63	31	NA	NA
Kasi et al (2019)	Anti cancer and supportive medications in cancer care / adult colorectal cancer patients	Retrospective cohort study	155	41	56	27	"at least 1 per pt"	NR
Patel et al (2021-b)	Supportive medications in cancer care / adult ambulatory cancer patients	Retrospective cohort study	0	NA	NA	NA	NA	NA
Reizine et al (2023)	Supportive medications in cancer (Opioid specific) /oncology patients with exposure to opioids	Retrospective cohort study	105	58	61	NR	NR	NR
Sakon et al (2024)	Supportive medications in cancer / paediatric and young adults with leukaemia	Retrospective cohort study	13	NR	NR	NR	NR	NR
Bhatt et al (2023)	Anti cancer and supportive medications / general oncology	Survey - Qualitative study (survey of health professionals)	NA	NA	NA	NA	NA	NA

Table 2: Characteristics of Included Stud

3.1.1 Study designs and settings

There was a heterogeneity of trial designs reported. Studies were conducted in America (8 studies), Australia (2 studies) and New Zealand (1 study). No studies were retrieved from the UK. None of the studies reported any significant barriers or challenges in recruiting either clinicians to implement a change in practice, or patients to take part in the studies.

3.1.2. Participant Demographics (of those who had a PGx test)

A total of 550 participants had a PGx test across 8 of the 11 studies. 1 study referenced blood taken for genetic analysis, but did not detail any further (19). Mean age was reported in 7 of the 8 PGx testing studies, with a range from 56 – 65. Sex was reported in 7 studies, and was evenly distributed, 1 study exactly 50% female participant, 3 with less than 50%, 3 with more than 50%.

Only 4 studies either gave a direct report of a drug-gene interaction (DGI) ratio, or provided sufficient information to calculate this. The 2 single-gene CYP2D6 studies reported a 50% (cyclizine) and 30% (opioid) actionable result percentage. Of the two multi-gene studies one tested 14 genes in 100 participants, reporting a DGI of 4.6, and one tested 27 genes in 155 participants reporting “at least 1 DGI” per participant.

3.1.3. Pharmacogenomic testing approach

In the 6 studies where a PGx test result was explicitly described, 2 studies were single-gene (both with the pharmacogene CYP2D6 being the object of interest) and the other 4 were multiple-gene or “panel” tests, with between 9 and 31 different pharmacogenes tested, all of which also including CYP2D6.

3.1.4. Therapeutic categories

All studies were of supportive care medications (SCM) in a palliative care context, with 4 being opioid specific, 1 cyclizine specific and the rest considering all SCMs

3.1.5. Studies reporting outcomes

Only 4 studies had sufficient information to describe the Patient Group, Intervention, Comparator arm and Outcome measures (PICO). Table 3 details the PICO information for these studies, as well as the main reported outcomes, and any notable comments on methodology.

Table 3: Studies Reporting Outcomes

Reference	Population	Intervention	Comparator	Outcomes measure(s)	Summary of outcomes	Review notes
Bull et al (2022)	Supportive medications in palliative care / palliative patients with chronic pain requiring daily morphine at ≥20 mg or equivalent for ≥1 week, and the chronic use of ≥4 nonopioid medications.	Multigene PGx test and report via MedWise system interpreted by Pharmacist and summary of recommendations passed to clinician	Pre/post assessment	Clinician satisfaction questionnaires, clinician acknowledgement and adherence to advice, Patient scores - Functional Assessment of Chronic Illness Therapy for Palliative Care (FACIT-Pal), Numerical Rating of Pain Scale (NRS), patient satisfaction questionnaires	Majority of clinicians agreed report both easy to use and improved quality of care. Clinicians accessed report routinely, and 55% of patients had one or more drug changes made, whilst 96% had at least one possible drug-gene interaction noted. Minor change in FACIT-Pal and NRS scores only.	This was a feasibility study (of delivery of a new PGX practice), so not designed to evaluate any change in patient reported scores, but reassuringly no ADRs or hospitalisations during study
Mosley et al (2023)	Supportive medications in cancer / oncology patients	CYP2D6-genotype guided opiod selction, with clinical recommendations	Usual Care	Brief Pain Inventory Short Form (BPI-SF), MD Anderson Symptom Inventory (MDASI), clinician acknowledgement and adherence to advice	No difference in baseline composite pain score or symptom severity between groups. Clinician acknowledgement 24%, and action on advice 18%	Genotyping failed on first attempt for 5/38 pts in active group leading to longer average turnaround times for results
Patel et al (2021-a)	Supportive medications in palliative care (Opiod specific) /cancer patients with uncontrolled pain at baseline	Multigene PGx test and report via by Pharmacist with summary of recommendations passed to clinician	Pre/post assessment pain and historic usual care cohort	2 point improvement in pain scores (0-10scale), opiod prescribing, clinician acknowledgement and adherence to advice	Pain score improved by ≥2 in 56% (PGx group) vs 30% (historic cohort)	Secondary analysis showed in those with PGx actionable genotypes pain score improved a non-significant amount vs not actionable (61% vs 53%). Small sample size, and non randomised
Kasi et al (2019)	Anti cancer and supportive care medications / adult colorectal cancer patients	Multigene PGx test and report via by Pharmacist with summary of recommendations passed to clinician	Pre/post assessment	Average number per patients of potential supportive care medication DGI warning (i.e. not linked to current prescriptions)	Average per patient of 34 (40%) out 86 potential supportive care medication DGI warnings	This study also reported number of DGI to colorectal chemotherapy which is beyond the scope of this review. Study not equipped to measure serial QOL or pain scores

In 3 of these 4 studies, a multigene PGx test was conducted, where the PGx results were reported via a proprietary system and then interpreted by a pharmacist before being passed to the clinician. (20-22) In the first of these studies, most clinicians agreed the report was both easy to use and improved quality of care. Clinicians accessed reports routinely, and 55% of patients had one or more drug changes made, whilst 96% had at least one possible drug-gene interaction noted. This study was not powered to detect a difference in patient outcomes pre and post assessment; and only minor changes in pain and functional assessment scores were detected. (20).

In the second of this style of study, it was reported that a 0-10 pain score improved by ≥2 in 56% (PGx group) vs 30% (historic cohort), although a secondary analysis showed that in those with PGx actionable genotypes pain score improvement was by a non-significant amount compared to that of the not actionable group (61% vs 53%). Of note, this study had a small sample size, was not randomised, and was set up to establish feasibility, rather than powered to prove efficacy of PGx. (21)

In the third of this style of study, the report gave "red" and "yellow" card severity warnings in its report for different medications. The average combined number of red and yellow warnings per patient was 34 out 86 potential supportive care medication DGI warnings, i.e. 40%. This study also reported that a significant DGI was found for common colorectal chemotherapy agents, which is beyond the scope of this review. Again, this study was not powered to detect changes in patient reported measures, and in fact was not equipped to collect measures of serial quality of life (QOL) or pain scores. (22)

In 1 of these 4 studies, a randomised (non-blinded) trial design of single-gene PGx (CYP2D6 and opioid choice) it was reported there was no difference in baseline composite pain score or symptom severity between groups (Brief Pain Inventory Short Form (BPI-SF), MD Anderson Symptom Inventory (MDASI). Both clinician acknowledgement (24%), and adherence - documented action on advice (18%) were low. Of note, genotyping failed on first attempt for 5/38 pts in the active arm, leading to longer than expected average turnaround times for results, which may have impacted on adherence to advice. (23)

3.1.6. Summary Narrative themes extracted

This scoping reviewed aimed to identify how pharmacogenomics could improve symptom management and supportive care. Our synthesis identified 5 relevant considerations for application to UK practice, and areas for future research.

Relevance to Supportive and Palliative Care

Studies have demonstrated that PGx is relevant to the medications used in a palliative and supportive care context. For example, a US based, retrospective study of 6985 cancer patients requiring SCM aimed to determine the proportion of patients with potentially actionable pharmacogenomic variants. (24) This study found that 24% (679/ 2760) in the population in question would be expected to have altered metabolism or drug response.

A prospective Australian study of 54 patients with cancer related pain found ten statistically significant associations between gene variants and opioid outcomes (opioid dose, pain scores, and/or adverse effects). (25)

A retrospective observational study of supportive care in leukaemia (for children and young people up to the age of 30) 82% (582/714) received 5 or more PGx drugs over their disease course and those with recurrent leukaemia had significantly more PGx drugs prescribed than those without. Adults with leukaemia received, on average, 10 PGx drugs. (17)

For both prevalence studies, it was not possible to report on drug and/or symptom control efficacy based on genotype, so whilst the frequency of PGx is high in this population group, the relevance of high PGx prescribing rates on effectiveness of supportive care is not known. In a study of PGx in palliative care, 15/43 patients who underwent PGx testing were found to have an actional genotype for prescribing modification, the most common of which was CYP2D6 (n- 13/15). (26)

The frequency of CYP2D6 phenotypes were 79% normal, 9% intermediate, 7% poor, and 5% rapid metabolisers. Whilst those with actionable genotypes were reported as having a higher pain improvement than others, this was not statistically significant (p=0.12). More research is needed to understand whether the application of PGx information improves outcomes in palliative and supportive care.

Choice of Targeted Drug/Gene Interaction in Supportive and Palliative Care

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is a US based group which produces evidence-based practice guidelines to support clinical decision making, where gene variations may affect the effectiveness of a medication. (27) Over 20 drugs related to palliative and supportive care have available CPIC guidelines to guide prescribing in the presence of genetic polymorphisms (Table 4). No such equivalent body exists in the UK, although pharmacogenomics is recognised as a strategic priority by NHS England. (28)

Table 4: Drugs with CIPC Guidance

Gene	Relevant Drug
CYP2D6	Ondansetron, oxycodone, tramadol, hydrocodone, codeine, methadone, cyclizine, trapisetron, nortriptyline, venlafaxine, metoclopramide
CYP2C19	Amitriptyline, Citalopram, escitalopram, omeprazole, pantoprazole, diazepam
CYP2C9	Celecoxib, meloxicam, piroxicam, ibuprofen

The CYP2D6 genotype is implicated to varying extents in the metabolism of many opioids, such as codeine, tramadol, hydrocodone, oxycodone and methadone. (5). Genetic variations in CYP2D6 may result in increased enzyme activity (with increased toxicity risk) or reduced enzymic activity which may limit analgesic effect. One study demonstrated that 84% of patients receiving supportive care in care received a drug metabolised by CYP26D, most commonly hydrocodone (40.4%), ondansetron (35.6%), oxycodone (24.2%) or tramadol (7.1%) (24)

CYP2D6 is implicated in the metabolism of cyclizine. It is thought that CYP2D may play a role in the metabolism of cyclizine to the inactive metabolite norcyclizine. Vella-Brincat et al investigated the pharmacokinetics of subcutaneous and oral cyclizine administration in a palliative care population. (29) Whilst a statistically significant difference was observed between metabolizers on cyclizine to norcyclizine ratio, there was no observed difference in nausea or drowsiness. (29)

Whilst CYP2D6 is the gene most studied, the relevance of the genotypes and phenotypes for CYP2B6, CYP2C19, CYP2C9 and SLC6A4 on symptom management is also considered in the literature. (24) These are implicated in medications used in supportive and palliative care such as methadone, sertraline, hydrocodone (used less commonly in the UK) and escitalopram.

In one study information regarding OPRM1 gene (which encodes the mu-opioid receptor) and COMT were determined, although these data were considered exploratory and not incorporated into the pharmacist supported decision support aid intervention used in the study. (20) This is a potentially important genotype, however as presence of a base-pair substitution in the gene coding OPRM1 may require 60% to 100% higher morphine doses for equal analgesia. (20)

Pharmacogenomic testing to guide supportive care management choices does not need to be independent of an existing cancer plan. Multi-panel PGx testing at diagnosis to guide both cancer treatment (e.g. irinotectan [UGT1A1] and fluorouracil [DPYD]) and supportive care (CYP26 and CYP2C19) has been shown as feasible in the management of people with metastatic colorectal cancer, to avoid drug-related adverse effects and improve quality of life. (30) Understanding the optimal point in clinical pathways to undertake PGx testing to guide symptom management is an area that requires further exploration.

Understanding the Potential Impact of PGx in Supportive and Palliative Care

Whilst previous CPIC guidance has suggested prescribing modifications based on any CYP2D6-metabolised opioid (including oxycodone, hydrocodone, codeine, tramadol and hydrocodone), the latest CPIC guidance only provides PGx based therapeutic recommendations for codeine and tramadol. (CPIC) This means that current PGx prescribing guidance is limited to moderate strength opiates only, implying a greater application to supportive / early generalist palliative care rather than more specialist pain control management.

For example, in a prospective pilot study of multi-gene PGx testing in outpatient palliative care in cancer, over half of patients had actionable genotypes that could be used to guide opioid management, although the results showed no observed difference in pain improvement between those with and without actionable genotypes. (21)

Beyond analgesia, PGx in SCM may affect the incidence or severity of adverse outcomes. A retrospective analysis of 61,572 adult oncology patients who had undergone PGx testing demonstrated that those with intermediate or poor metaboliser phenotype were significantly more likely to experience pain related hospital encounters and were more likely to be treated with “later line” opioids than normal metabolisers. (31) No studies reported any health economics analysis of a PGx pathway vs standard care. More work is needed to understand the impact of genetic variation on healthcare usage and expenditure towards the end of life, and the potential impact that PGx could have on mitigating this in a UK context.

Acceptability of Testing in a Supportive and Palliative Care Context

PGx testing is commonly undertaken via a buccal swap; a procedure which takes seconds. Studies of PGx testing in palliative care population has demonstrated a high level of acceptance; for example in one study 76% of patients approached agreed to take part and even higher levels (up to 95%) seen in

non-cancer settings. (23, 32) Reliability of genotype testing is reportedly high, with a success rate of 95% for testing.

Buccal testing relies on adequate saliva production and may not be universally acceptable, for example in the presence of mucositis. In an acute setting, PGx testing via blood samples may be equally as effective and acceptable, although at present there is no evidence to guide decision making between testing methods.

Patients will palliative and supportive care needs have demonstrated a willingness for involvement in PGx clinical trials. In a study which aimed to establish a clinical PGx registry, which linked clinical phenotype and biological/genetic information (but did not involve a specific prescribing intervention), 63% (58/92) of eligible participants consented to involvement, with researchers commenting: *'I thought the patients were surprisingly receptive to this. I never imagined that the populations that were very close to death would entertain the idea. But they have.'' (Clinical trial nurse).* (19) In post study interviews participants themselves rated high levels of satisfaction, finding it a relief from boredom and a highly relevant topic *''It is fascinating to be involved so early in the research. The project as a whole –bloods, questionnaires – are not an issue at all. The proposal captures a really important need that is so obvious.''* (19)

Changing Prescribing Behaviour

To realise the potential benefits of PGx, knowledge of a gene-drug interaction must be translated into a change in prescribing practice. In one trial that formally reported on this metric (an implementation clinical trial of CYP2D6 guided opioid therapy for cancer pain), only 18% (2/11) of patients who had genotype-guided recommendations had a change congruent with recommendations. (23)

This study highlights the importance of "*human factors*" in considering the effectiveness of pharmacogenomic testing; if prescribing behaviour is not influenced by the results, or clinical recommendations are unclear, identification of genetic variants will not translate to improvement in pain and/or symptom management. Potential barriers to clinical implementation are delays in obtaining actionable results, reluctance to change a recently developed pain management plan when results become available and/or lack of familiarity with PGx. Involvement of a clinical pharmacist to highlight relevant gene-drug interactions and to provide ongoing medication support might be used to support implementation. (33)

A prospective, single arm feasibility trial conducted with palliative care providers aimed to determine to what extent clinicians would access and use a PGx decision support system. This study showed evidence of clinician engagement, with the PGx information being used to change prescribing practice in 55% of cases, but also that 85% of clinicians either "agreed" or "strongly agreed" that pharmacogenomic testing improved the quality of care. (20)

Given the heterogenicity of supportive and palliative care services across the UK, further work is needed to understand how a PGx service, if effective and acceptable, could be safely and consistently applied across the various settings in which this care is delivered, and how the education needs of clinicians could be best met.

4. Discussion

Clinical trials have failed to yield definitive evidence that the PGx testing can improve symptom control in a palliative care context. We did not find any UK based studies into the use of PGx and SCM in supportive and palliative care in cancer. Evidence from elsewhere (predominantly North America) suggests that is it both feasible and acceptable to patients and clinicians to conduct PGx in a supportive and palliative care setting. Many palliative care patients are prescribed SCMs that are amenable to PGx test results, and when multigene PGx testing is carried out there is at least 1 DGI per patient. Clinician acknowledgement of and adherence to recommendations is variable, and it has yet to be conclusively demonstrated that PGx testing produces tangible therapeutic benefit, such as enhancing patient outcomes, e.g. improvements in pain scores. Furthermore, any potential benefits from PGx testing must be demonstrably cost effective in a UK context; this evidence is widely lacking due to lack of European trials in this area.

To fully understand the potential benefits of PGx in supportive and palliative care in cancer, there is a need for UK-based prospective clinical studies. Use of pragmatic PGx trials may also be important to evaluate the feasibility of integrating PGx testing into clinics, as services providing supportive care may demonstrate significant variation. (33) Experience from the US suggests that once health care providers become aware of PGx implementation in one aspect of care, they are much more likely to be open to exploring it's use in other domains. (34) It remains to be seen whether the UK will follow suit.

Limitations

We chose a scoping review structure restricted to primary evidence to identify gaps in knowledge of the use of PGx in supportive and palliative care, and to generate future research questions. It is possible that this strategy may have missed finding evidence of use to this topic from review articles, conference abstracts and sources within the grey literature. Also, given the paucity of trials to date, there may well be generalisable answers to questions of cost efficiency in using PGx, which is an important consideration for any future intervention.

We note that ethnicity is a major factor in PGx, with well documented differences in genetic variation of CYP2D6 amongst other genotypes being relevant. This was under reported in the studies we examined, and so we were unable to comment on any relevant finding. Future studies should consider the relevance on ethnicity to PGx interventions.

5. Conclusion

How can PGx improve symptom management in supportive and palliative care? Using the information derived from this review, it is evident that knowledge of genetic polymorphisms may help clinicians understand why a supportive care medication has been less effective than anticipated in the palliative care setting. It is both feasible to conduct PGx testing in this patient group, and that such testing derives a high yield of PGx actionable genotypes. However, to date, there is no published evidence to demonstrate conclusively that PGx improves symptom control in supportive and palliative care. Furthermore, recent changes to CPIC guidance suggests that role of PGx in pain management is likely to be more relevant to early supportive care, given the current absence of PGx-guided recommendations for strong opioids.

The drug-gene interactions most relevant to supportive and palliative care are likely to include CYP2D6 and opiates/anti-emetics, CYP2C19 and anti-depressants/protein pump inhibitors and CYP2C and non-steroidal anti-inflammatory drugs.

This is a paucity of published trials to understand what implementation models for PGx might improve symptom management in supportive and palliative care. Given the absence of positive findings from most of the trials, there was no one single preferred implementation approach identified, and therefore it is not possible to describe a superior trial design or implementation model, based on this review. Similarly, with respect to pain control, there were no substantive conclusions to the question of the extent and type of evidence of pharmacogenomic testing (PGx) in supportive and palliative care, as no study was powered to detect any such clinical improvements, and no study conducted a health economics analysis.

Despite this, the evidence presented suggests that PGx may have a (yet to be defined) role in symptom management in supportive and palliative care; given the prevalence of PGx actionable genotypes across all studies and relevance to many commonly used SCMs.

Perhaps the most significant finding, is the role that human factors may play in PGx, with specific gaps in training needs identified, and the need to identify a way in which to translate information on potential PGx actionable genotypes into action by clinicians. Understanding how to influence prescribing behaviour will be critical to the success of any prospective PGx intervention, particularly given the known variation in supportive and palliative care services.

We would advocate that future research needs to be conducted to determine:

- Can PGx-guided prescribing improvement symptom management in supportive and palliative care?
- What delivery approach should future PGx services for supportive and palliative care use? Which drug-gene examples should be considered “core” to a panel test for palliative and supportive care in cancer?
- What is the optimal way for a PGx test report to translate into clinical action?
- What are the clinical and/or health economic benefits to introducing PGx testing in supportive and palliative care in the UK setting?

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Author contributions

Designing the scoping review protocol and developing the search strategy: CB and MP. Conducting the literature search, screening and data extraction: CB and MP.. Contributing to the synthesis of results: CB and MP. Providing critical revisions and overseeing the writing and finalisation of the manuscript: CB and MP. MP is responsible for the overall content of the manuscript and acts as the guarantor.

Conflicts of interest

We have nothing to declare.

Ethics Approval

Not required

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Figure Legend:

PRISMA flowchart summarising the process of selecting and excluding data