A Systematic Review and Analysis of the Use of Polygenic Scores in Pharmacogenomics

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Polygenic scores (PGSs) have emerged as promising tools for complex trait risk prediction. The application of these scores to pharmacogenomics provides new opportunities to improve the prediction of treatment outcomes. To gain insight into this area of research, we conducted a systematic review and accompanying analysis. This review uncovered 51 papers examining the use of PGSs for drug-related outcomes, with the majority of these papers focusing on the treatment of psychiatric disorders (n = 30). Due to difficulties in collecting large cohorts of uniformly treated patients, the majority of pharmacogenomic PGSs were derived from large-scale genome-wide association studies of disease phenotypes that were related to the pharmacogenomic phenotypes under investigation (e.g., schizophrenia-derived PGSs for antipsychotic response prediction). Examination of the research participants included in these studies revealed that the majority of cohort participants were of European descent (78.4%). These biases were also reflected in research affiliations, which were heavily weighted towards institutions located in Europe and North America, with no first or last authors originating from institutions in Africa or South Asia. There was also substantial variability in the methods used to develop PGSs, with between 3 and 6.6 million variants included in the PGSs. Finally, we observed significant inconsistencies in the reporting of PGS analyses and results, particularly in terms of risk model development and application, coupled with a lack of data transparency and availability, with only three pharmacogenomics PGSs deposited on the Polygenic Score Catalog. These findings highlight current gaps and key areas for future pharmacogenomic PGS research.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Polygenic scores (PGSs) represent effective tools to improve the accuracy of disease risk-based screening programs. However, limited information exists for the use of these scores in pharmacogenomics.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This systematic review aimed to provide a comprehensive overview of current strategies that are being applied to examine the use of PGSs in the context of pharmacogenomics.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ We provide an overview of innovative PGS analyses that are currently being applied in the field of pharmacogenomics, including which areas show promise for implementation in the clinic. Current limitations include Eurocentric biases, poor adherence to PGS reporting guidelines, and gaps in data availability and transparency.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ We have highlighted a need for large globally representative pharmacogenomic studies and consortia to uncover clinically actionable findings, which will lead to improved treatment outcomes.

Complex human phenotypes are influenced by several genetic and environmental factors.¹⁵ Polygenic scores (PGSs) represent ideal tools to estimate individual risk for complex traits. These scores sum up the combined effects of several genetic variants into a single score, which can be used to predict genetic predisposition for a phenotype.⁶⁻⁸ In line with this, recent research has highlighted the

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The clinical utility of PGSs across disease areas and applications, particularly in risk-based screening programs,\textsuperscript{9,11} For example, the risks conferred by a PGS for coronary artery disease have been shown to be comparable to those of rare, highly penetrant, disease-causing variants, but are superior in their generalizability to the broader population.\textsuperscript{7} Further, the implementation of a PGS for the prediction of osteoporotic fractures was successful in reducing unnecessary and expensive testing procedures by 41%.\textsuperscript{12} With decreasing costs of genotyping technologies, it is now economical to generate genome-wide genotype data for individuals, and these data can be used to infer polygenic risk for hundreds of health-related traits.\textsuperscript{8,13}

One area where the application of PGSs would be of great value is the field of pharmacogenomics, the study of how genetic variants impact individuals’ responses to drug treatments.\textsuperscript{14-17} For any pharmacological therapy, users may experience a range of physiological reactions, including nonresponse and adverse drug reactions (ADRs). These nonoptimal treatment outcomes can have long-lasting consequences on the quality of life of patients.\textsuperscript{18} Importantly, a portion of the variability in treatment response outcomes can be attributed to genetics.\textsuperscript{19,20} In incidences where genetics plays a significant role in predicting drug response, pharmacogenomics may be implemented in clinical practice to guide treatment decisions in order to maximize effectiveness and minimize harm.

While genome-wide association studies (GWASs) have been successful in identifying genetic variants that are associated with drug treatment responses, in many cases, the effects of individual genetic variants are small.\textsuperscript{21} Therefore, individually, these genetic variants are limited in their ability to provide clinically meaningful predictions of treatment outcomes. The inclusion of PGSs into prediction algorithms may aid in improving the accuracy of these predictions. However, while the use of GWASs in pharmacogenomics has recently been reviewed,\textsuperscript{21} to the best of our knowledge, there are currently no publications which have reviewed the evidence available for the use of PGSs in the context of pharmacogenomics as a whole.

We therefore performed a systematic review and analysis of studies that have used PGSs in the context of treatment response phenotypes. Through this review, we sought to provide an in-depth analysis of how PGS research is being applied in the field of pharmacogenomics. We also sought to examine whether these findings are of relevance to populations around the globe and whether reporting is sufficient to ensure reproducibility of findings. Through summarizing these data, we aim to provide an overview of pharmacogenomics PGS research, including current gaps and future avenues of research and applications.

METHODS

Prior to initiating data collection, we registered our review protocol on International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42021366072).\textsuperscript{22} Reporting follows the 2020 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.\textsuperscript{23}

Search details

Our review aimed to summarize and critically analyze the use of PGSs in pharmacogenomics, including drug types pertaining to any disease. We used broad inclusion and exclusion criteria to achieve this goal such that any original research article using PGSs in relation to drug-related outcomes was included in our systematic review. A PGS was defined as “a single value estimate of an individual’s genetic liability to a phenotype, calculated as a sum of their genome-wide genotypes, weighted by corresponding genotype effect estimates derived from GWAS summary statistics.”\textsuperscript{24} PGSs that used unweighted effects, and those derived from candidate gene studies, were excluded. PGS studies that examined therapeutic drug-related outcomes and ADRs were considered to have drug-related phenotypes and were included. Studies that did not use pharmacological treatments were excluded (e.g., radiotherapy, supplements, surgery, or any nondrug psychiatric therapies such as cognitive behavioral therapy). We excluded non–English-language publications due to resource constraints. Conference abstracts were excluded as they did not contain enough information to extract PGS details and assess study quality.

We searched the Medline and EMBASE databases on February 18, 2021 using the search criteria outlined in Table S1. This search strategy was modeled based on search criteria used by other reviews of PGSs.\textsuperscript{9,10,11,24,25}

Study selection

Literature screening was performed by two independent reviewers (D.J. and M.A.P.W.) in three separate stages of screening: title, abstract, and then full text. Each reviewer compiled a data sheet containing information on whether an article should be included or excluded, including reasons for exclusions. These results were subsequently compared in R (version 4.0.3, Vienna, Austria).\textsuperscript{26} and in the case of disagreements, an independent review was performed by a third reviewer (B.I.D.). Remaining unresolved discrepancies were discussed as a team (D.J., M.A.P.W., B.I.D., and G.E.B.W.). Criteria for inclusion and exclusion for title, abstract, and full-text screening are detailed in Table S2.

Data extraction

Data extraction was performed by three authors (D.J., S.M.L., and B.I.D.), with each article examined by at least two authors. During the detailed data extraction process, additional articles were flagged for discussion as they did not meet all the inclusion criteria. Decisions to exclude these articles were made as a team (D.J., M.A.P.W., B.I.D., G.E.B.W., and K.K.). A standard data extraction form was developed and used for the final 51 articles. The form was piloted on five papers and changes were made before being applied to the remaining papers. We extracted details of first and last authors and their institutions using the easy-PubMed R package.\textsuperscript{27} Only the first institution for each author was used. Papers were categorized by disease area according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10\textsuperscript{th} Revision).\textsuperscript{28} Drugs were classified by the Anatomical Therapeutic Chemical (ATC) Classification system.\textsuperscript{29} Details of base cohorts, target cohorts, and validation cohorts were extracted, along with details relating to PGS construction and analyses. Base cohorts were defined as the cohorts which were used to generate GWAS summary statistics (i.e., effect sizes and P values) to base the PGS’s calculation on.\textsuperscript{5} Target cohorts are defined as those cohorts in which the PGS was developed and tested, while validation cohorts are defined as those in which the PGS was independently validated.\textsuperscript{6}

A detailed analysis of ancestry in each cohort was performed, using the ancestry categories for pharmacogenomic research specified by Huddart et al. (2019) (American, Central/South Asian, East Asian, European, Near Eastern, Oceanian, and Sub-Saharan African, African American/Afro-Caribbean, and Latino).\textsuperscript{30} Categories for “Asian” and “African” were used when specific ancestry categories from Huddart et al. could not be identified based on individual study details. If ancestry was stated as “Black” and the study recruited in North America, we recorded ancestry as “AAC African American.” Romani people were recorded as South Asian.\textsuperscript{31} In cases where the base cohort ancestries were not stated in the article, this information was extracted from the original study which first described the base cohort.
In order to draw comparisons between the pharmacogenomic PGSs included in this review and PGSs used more generally in human genetics, data from the Polygenic Score Catalog was downloaded on November 24, 2021.²³,³³ PGSs that were already included in the current review (n = 3) were excluded from the Polygenic Score Catalog data and details relating to the number of individuals included in score development and evaluation, as well as the number of variants included in the PGSs, were extracted.

PGS reporting standards

There is no standard quality or risk of bias assessment tool for PGS systematic review.³⁴ Therefore, we used the recently published PGS-reporting criteria of Wand et al. (2021) to evaluate how well articles adhered to reporting guidelines.³⁴ We opted to focus on articles published in the most developed areas of pharmacogenomics PGS research and therefore only included articles falling into disease areas with more than five publications. The reporting standards described by Wand et al. were independently assessed by three authors (M.A.P.W., S.M.L., and B.I.D.) for each of these articles. These reporting standards examined the level of detail provided for the study background, the study population and data, risk model development, and application and evaluation of the risk model, as well as the limitations and clinical implications of the PGSs. The information required for each of these categories is detailed in Table 1 and the Supplementary data of Wand et al.³⁴ Each category was graded as “yes,” “no,” “somewhat,” or “not applicable” according to the extent to which the paper captured the relevant information. Consensus grades (i.e., as determined by at least two of the three reviewers) were included in downstream analyses. Cases where the three reviewers disagreed on the grading were resolved through discussion as a team (M.A.P.W., S.M.L., and B.I.D.). In addition, to determine data transparency and availability, all included papers were examined by two authors (M.A.P.W. and S.M.L.) to determine if summary statistics were publicly available, available upon request and/or if the tested PGSs were included in the Polygenic Score Catalog database.³²

Synthesis of results

Analyses were performed using R (version 4.0.3)²⁶ via RStudio,³⁵ and figures were plotted using the ggplot2³⁶ and ggmap³⁷ R packages. The mean, range, median, and interquartile range for the number of individuals included in base and target cohorts was calculated for both the pharmacogenomic PGS articles included in this review, and the articles deposited within the Polygenic Score Catalog.

RESULTS

Overview of main findings

Our initial search identified 1,909 articles for screening for inclusion. A total of 1,847 remained after removing duplicates, as well as non–English-language articles. After screening by title and abstract, 93 papers were retrieved for full-text screening. After screening by full text, 59 papers were selected for inclusion. A further 8 papers were excluded during data extraction, as they did not meet the criteria for drug-induced phenotypes or genome-wide PGSs, leaving a total of 51 papers for inclusion in our systematic review (Figure 1).

Included papers (Table S3) were published between 2013 and 2021, with the number of articles examining the use of PGSs in pharmacogenomics steadily increasing over this time (Figure 2). Examination of these publications revealed that the most common ICD-10 disease area was in the field of mental and behavioral diseases (Figure 2a, n = 30 papers out of 51, total = 59%). Other highly represented disease areas were the circulatory system and the digestive system. Correspondingly, the most common type of drug examined was ATC code N (nervous system) (Figure 2b). The ATC code was not present for one drug (evacetrapib) which has since been withdrawn from market.³⁸ The 51 articles examined 105 drug phenotypes, with 23 relating to ADR phenotypes and 82 relating to drug efficacy or response. Full details for these studies are summarized in Table S3. Effect sizes and P values on which the PGS calculation was based, were obtained from base cohorts whose phenotypes fell into three distinct categories—pharmacogenomic phenotypes (e.g., drug-induced phenotypes), phenotypes related to the disease that was being treated (e.g., schizophrenia GWAS data was used for the development of an antipsychotic response PGS), or phenotypes related to the ADR under investigation (e.g., obesity GWAS data was used for the development of an antipsychotic-induced weight gain PGS) (Table S4).

Overview of methodology used

Given that large cohorts are required for accurate effect size estimates of risk alleles for PGSs, we examined the sample sizes included in base cohorts (i.e., cohort used to generate summary statistics to obtain risk variant effect sizes and P values to inform PGS calculations) and target cohorts (i.e., cohort in which the PGS is developed and tested). The median sample size in the base cohorts was 150,064, while the median sample size of the target cohorts was 796—nearly 200-fold smaller than the base cohort median sample size. In comparison, while the median sample size of base cohorts included in the Polygenic Score Catalog was smaller than

| Table 1 Base and target cohort size comparisons |
|-----------------------------------------------|
| Pharmacogenomic systematic literature review (n = 51) | Polygenic Score Catalog (n = 245) |
| Mean (range) | Median (IQR) | Mean (range) | Median (IQR) |
| Base cohort size³ | 205,248 (95–1,131,881) | 150,064 (36,090–332,820) | 104,957 (41–1,474,097) | 34,195 (6,565–166,988) |
| Target cohort size⁵ | 1,523 (44–12,678) | 813 (301–1,378) | 52,187 (38–1,473,098) | 7,821 (3,220–60,591) |

Base and target cohort sizes included in PGSs for this pharmacogenomic systematic literature review compared with those included in the Polygenic Score Catalog. Base cohort: cohort used to generate summary statistics to obtain risk variant effect sizes and P values to inform PGS calculations.⁵Target cohort: cohort in which the PGS was developed and tested.⁶IQR, interquartile range; PGS, polygenic score.

³ Corresponding variable in the Polygenic Score Catalog was the Source of Variant Associations (i.e., cohort in which the original genome-wide association study was performed).⁵Corresponding variable in the Polygenic Score Catalog was the Score Development/Training and Evaluation sample sets.
that of the pharmacogenomic PGS studies, the median sample size of the target cohorts was approximately 10-fold higher than used in the pharmacogenomic PGS studies (Table 1).32

The samples included in these studies were genotyped with a wide variety of arrays; however, imputation was performed in most cases, with 69% of studies using the 1000 Genomes Project data as a reference for imputation. Similar to the studies included in the Polygenic Score Catalog, standard quality control steps were applied to remove low-quality variants and samples, as described in more detail by Choi et al. (2020).6 Given that not all variants will contribute to pharmacogenomic traits, methods to determine which variants should be included in the PGSs are important. While shrinkage of effect estimates using various statistical methods is used frequently for the development of PGSs (reviewed in more detail by Choi et al. (2020)6), the majority of pharmacogenomic PGSs used P value thresholds to determine which variants were included in the PGSs. There was a wide range in P value thresholds that were used to determine which variants were included in the final PGSs. The justification for P value threshold selection differed among the various studies. Some articles selected a P value threshold a priori, while others based their selection according to the performance of the PGSs. The respective articles included between 3 and 6,600,000 variants in their final PGSs. These values were similar to the number of variants included in PGSs recorded in the Polygenic Score Catalog, which ranged from 2 to 6,917,436 variants.32

As variants are often inherited together, it is important that linkage disequilibrium (LD) between variants is accounted for. LD acts as a measurement of the correlation between two given alleles. While LD can be accounted for in shrinkage methods (reviewed in more detail by Choi et al. 2020),6 the majority of studies included in this review used LD clumping, which reports on the most significant genetic associations within a region of smaller groups of genetically linked variants. Several different programs (LDpred, LASSO

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![Figure 1](https://wileyonlinelibrary.com)
regression, PLINK, GCTA-GREML, PRS-CS, PRSice and R) and methods were used to perform the PGS analyses; however, PLINK or PRSice were used in 82% of the analyses (Table S3). In comparison with studies deposited into the Polygenic Score Catalog, many different programs (LASSO regression, LDpred, PRS-CS, GCTA-COJO, SBayesR, PRSice, snpnet, and SparSNP) and methods (LD clumping/pruning & P value thresholding, variants reaching genome-wide significance and regularized regression (elastic nets)) were used to perform PGS analyses.32 Of the studies that reported significant PGS findings (Figure 3), only five included validation cohorts, with sample sizes of these validation cohorts ranging from 433 to 5,616.39-43 There was only one study that performed functional validation. This investigation reported a significant association between a drug-induced liver injury (DILI)-PGS and fasiglifam-induced DILI, which was validated using primary hepatocytes and stem cell–derived organoids. This “polygenicity-in-a-dish” validation strategy showed that this PGS was predictive of DILI in patients.

**Figure 2** Number of papers (a) included in the systematic review classified by ICD-10 Disease area28 and (b) classified by ATC classification of included drugs.29 ATC, anatomical therapeutic chemical; ICD, International Classification of Diseases and Related Health Problems; incl, including. [Colour figure can be viewed at wileyonlinelibrary.com]
treated with fasiglifam, as well as amoxicillin-clavulanate and flucloxacillin.44

**Pharmacogenomic phenotypes included in current research and significant findings**

More than half of the articles included in this review focused on developing PGSs to improve antipsychotic ($n = 14$) and antidepressant ($n = 12$) treatment outcomes. Half of the articles focusing on antipsychotic response reported significant associations between PGSs derived from schizophrenia or major depressive disorder risk GWASs and antipsychotic response.42,45,46,47,48,49 Of the 12 studies examining antidepressant response outcomes, 4 reported significant associations.41,43,50,51 Two articles found that lower major depressive disorder PGSs and schizophrenia PGSs were associated with improved lithium response in bipolar disorder.52,53 In addition, an association between an attention deficit hyperactivity disorder PGS and attention deficit hyperactivity disorder treatment response was reported, but this PGS was based on a small base cohort ($n = 1,655$).54 Finally, one study tested the association between an obsessive-compulsive disorder PGS and treatment response; however, no significant association was observed.55

The second most common disease area for the application of PGSs was pharmacogenomic studies of the circulatory system ($n = 7$). Three articles examined the association between a PGS derived from a coronary artery disease GWAS and response to low-density lipoprotein lowering medications, with two reporting significant associations.38,56,57 Of the two studies that examined antihypertensives responses, only one study reported a significant association; however, the base cohort that was used to inform the PGS was small ($n = 248$).58,59 Finally, significant associations were reported for a PGS derived from a GWAS of QRS duration (electrical heart pattern) and Brugada syndrome/response to the antiarrhythmic agent ajmaline,60 as well as for a diverticular disease PGS and nicorandil intolerance (Table S5).61

A number of conditions were covered in the remaining 14 publications included in this review. Three articles examined PGSs in the context of the treatment of inflammatory bowel disease, with one of these studies reporting a significant association between...
mesalamine-induced allergy and a PGS based on a small GWAS of this ADR.\textsuperscript{62-64} Similarly, three articles were focused on the treatment of neoplasms, with one of these articles reporting a significant association between PGSs derived from GWASs of vitiligo, psoriasis, and atopic dermatitis and overall survival of bladder cancer in atezolizumab-treated patients.\textsuperscript{65-67} The remaining articles were focused on various efficacy phenotypes (response to antidiabetic medications,\textsuperscript{39} growth hormones,\textsuperscript{39,68} migraine therapeutics,\textsuperscript{40} and Kawasaki disease treatments\textsuperscript{69}) and ADR phenotypes (drug-induced liver injury,\textsuperscript{44} levodopa-induced dyskinesias,\textsuperscript{70} drug-induced fractures,\textsuperscript{44,71} and antiretroviral-induced weight gain\textsuperscript{72}). Significant findings were reported for all of these treatment outcomes, with the exception of the studies investigating response to growth hormones and antiretroviral-induced weight gain.

Global representation of research participants and authors
To determine whether research into the use of PGSs in pharmacogenomics is being performed equally across the globe, we extracted the institutions of the first and last authors for all 51 papers included in this review. The majority of articles have been led by groups located in North America, Europe, and Australia. No first or last authors were based in Africa or South Asia (Figure 4).

Extending these analyses further, we examined whether the research participants included in the studies were representative of the global population and whether there has been a shift in representation over the years. Examination of the ancestry of the base (Figure 5a) and target (Figure 5b) cohorts revealed that 91% and 72% of participants were of European ancestry, with a slight increase in diversity observed in both cohorts over time. There was no representation of Native American or Oceanian ancestries.

Adherence to reporting guidelines
To examine the adherence to the recently published reporting standards for PGSs,\textsuperscript{34} which can be reflective of the level of reproducibility of the study’s findings, we decided to focus on publications in the most developed areas of pharmacogenomics PGS research (i.e., mental and behavioral disease and circulatory system diseases). In general, most articles described the background with sufficient granularity (Figure 6). While details relating to the cohort demographics and ancestry were included in the main text in the majority of cases, in several instances, information relating to the recruitment period was missing when describing the study population. Details were usually provided for genotyping and imputation, including the reference populations and quality control metrics that were used, even though some of these data

![Figure 5](https://example.com/figure5.png)  
**Figure 5** Ancestries of participants in (a) base cohorts (BC) and (b) target cohorts (TC) over time. [Colour figure can be viewed at wileyonlinelibrary.com]
were embedded in the Supplementary Material or previously published articles. Although details were provided for the outcome of interest, information relating to the appropriate data transformations for downstream statistical analyses were often absent.

In contrast, areas relating to risk model development and application were less comprehensively described. While details relating to the inclusion and weighting of variants were well described, a large number of articles lacked information relating to risk model types and the measures used to assess performance. Similarly, while most articles provided information relating to whether the PGSs were significantly associated with the outcome of interest, including the overall performance of the PGSs (e.g., proportion of variance explained; $R^2$), very few other details were provided. Only a handful of articles provided information relating to whether the PGSs were normally distributed in the populations under investigation and very little information was provided relating to risk model discrimination or calibration.

In terms of discussing the relevance of PGS results, while many articles did include a limitations section, this was not always comprehensive and details relating to the interpretation, generalizability, and intended uses were absent in most cases. Finally, with regard to data availability and transparency, only 3 of the 51 PGSs (5.9%) that were included in the systematic review deposited their data in the Polygenic Score Catalog. As reproducibility of PGSs is extremely important, we also examined how many articles provided information outside of the Polygenic Score Catalog regarding the variants included in the PGSs (e.g., reference single-nucleotide variant identification, effect sizes, etc.) and found that an additional nine articles provided this information in their supplementary data. While these data were not provided for articles falling into categories relating to mental health and behavioral disorders, in the majority of cases PGSs were derived from data obtained from the Psychiatric Genomics Consortium (PGC), for which the summary-level data are easily accessible. As GWASs were performed in the majority of target cohorts, we also examined how many studies provided links to the pharmacogenomics target cohort GWAS summary statistics, and found that only seven articles provided this information. It is important to note that some articles, which cited research participant privacy issues, would provide data upon request.

**DISCUSSION**

This article describes the first systematic review of the use of PGSs in pharmacogenomics. Through this review, we gained insight into the current landscape of this clinically relevant research, including gaps that need to be addressed, and important avenues for future research. These findings are discussed in further detail below.

**Sample size limitations in current pharmacogenomic PGS research**

One consistent theme that emerged for the articles included in our review was the need for innovative analyses to circumvent the sample size limitations that are associated with pharmacogenomic GWAS cohorts. Analyses by Choi et al. have shown that for PGSs derived using information from base cohorts of 100,000 samples, between 200 and 500 samples are required in the target data set in order to obtain 80% power to predict traits with a range of heritability estimates ($h^2$: 0.11–0.23). Due to the difficulty in recruiting large cohorts of uniformly treated patients, for whom treatment outcome information is available, sufficient numbers of samples are often only available for target cohorts but not for base cohorts. Therefore, GWASs derived from large cohorts of related disease phenotypes were frequently used as a base data set to extract accurate effect size estimates for risk variants included in the development of PGSs. These included phenotypes related to the disease in which treatment response was being investigated (e.g., schizophrenia PGSs for the prediction of antipsychotic response) or phenotypes related to the ADR phenotypes under investigation (e.g., obesity PGSs for the prediction of antipsychotic-induced weight gain). While these strategies did uncover significant findings in some of the studies, these findings were not consistently replicated. This may be attributed to the fact that non–drug-related phenotypes only partially capture the true effects of pharmacogenetic variants, with drug exposures modulating the effects of these variants. Nonetheless, one study reported that the sensitivity and specificity of the PGS developed for ajmaline-induced type I Brugada syndrome was shown to be similar to other cardiac tests such as exercise electrocardiography. As genetic tests can be used to guide treatment decisions prior to treatment initiation, these findings highlight the unique advantage of using.
pharmacogenomic PGSs to prevent adverse outcomes without exposing patients to potentially harmful treatments.

**Biases in PGSs**

Other authors have commented on the Eurocentric bias in the development of PGSs in the broad field of human genomics.74-77 Our pharmacogenomic investigation corroborated this; the genetic ancestry of the populations included in this pharmacogenomics-focused review were overwhelmingly European (base cohort: 91% and target cohort: 72%) (Figure 5). As PGS development relies on the availability of GWAS data, the level of diversity within these genomic studies directly affects the applicability of the resulting PGSs to diverse global populations. In the context of PGSs aimed at improving the treatment of disease, unequal representation of the world’s populations can result in a widening of already existing health disparities.

Our analyses revealed that the observed Eurocentric bias may be largely driven by the location of the authors who are leading the research. In line with this, we showed that first and last authors were more likely to be located at institutes in Europe and North America (Figure 4). Collaborations that involve underrepresented populations should ensure that appropriate authorship opportunities exist for individuals from those countries and/or populations. Increased global representation of researchers will likely encourage the inclusion of more diverse participants, which will help to improve the generalizability of PGSs for diverse populations.74 However, if we are to achieve this goal, more funding will need to be allocated to resource-limited settings to ensure equal opportunities for the generation of globally representative large-scale genomics databases.

**Adherence to PGS reporting standards**

PGS research related to common human disease has only recently begun to gain momentum. This is particularly true in the context of pharmacogenomics. In line with the relative infancy of this field, examination of the 2021 Polygenic Risk Score Reporting Standards (PRS-RS),34 revealed that there are large inconsistencies in the way in which results for pharmacogenomic PGSs are reported. This may in part be attributed to a previous lack of reporting standards and a current lack of robust quality assessment tools for PGS research. In our systematic review, we found that patient cohorts and genotype analyses are generally well described. This is reflective of past pharmacogenomic research, where the use and reporting of GWAS results is standard practice. However, in contrast, details relating to PGS analyses and results are currently lacking. Finally, there are large gaps in data transparency and availability. In order to ensure that pharmacogenomic research adheres to current standards, it is important that summary statistics for pharmacogenomic GWASs are made publicly available and data relating to pharmacogenomic PGSs (e.g., risk variants and effect sizes) are deposited into the Polygenic Score Catalog. We strongly recommend that future publications adhere to the PRS-RS guidelines as improvements in reporting standards will facilitate the wider use of PGSs and ensure the reproducibility of findings.

**Recommendations for future pharmacogenomics research**

Given the actionability of clinically relevant pharmacogenomic findings, the use of PGSs in pharmacogenomics has a promising future. However, one of the main challenges to implementation is the difficulty in recruiting significantly large sample sizes to generate accurate PGSs.78,79 Current research is applying creative strategies, such as using GWAS data obtained from large cohorts of non-drug-related phenotypes (e.g., the UK Biobank,80 CanPath; canpath.ca), to develop pharmacogenomic PGSs.81 To increase the relevance of this research to drug phenotypes, future studies could examine the use of pharmagenic enrichment scores, coined by Reay and Cairns, to refine PGSs to specifically focus on variants within a pathway of known relevance to the drug of interest.82 Further, it is well known that genetic variation in drug-metabolizing genes, such as CYP2D6, plays an important role in treatment outcomes. However, this variation is poorly captured by current genotyping arrays, and consequently PGSs.83,84 Therefore, future research should investigate the role of PGSs in the context of variation affecting the function of well-known pharmacogenes (e.g., relevant drug-metabolizing enzymes), using already established methods for genotyping and metabolizer class classification. PGSs may be added to genotypically determined drug metabolizer activity scores to improve the accuracy of pharmacogenomic tests. Similar approaches have been described for the use of PGSs in breast cancer risk predictions,85 as well as the use of a weighted CYP2A6 genetic risk score to predict nicotine clearance.86

While these innovative analysis strategies have yielded novel findings, these data cannot completely make up for the lack of large pharmacogenomics-focused cohorts. Therefore, if the field is to advance to its full potential, it is of great importance that large consortia are formed to allow for the recruitment of the relevant large pharmacogenomic cohorts. These consortia should include researchers and participants from across the globe in order to increase the relevance of these results to global populations. In addition to obtaining large cohorts of research participants, it is also important to ensure that findings are validated. Replication of PGS findings could be achieved using data from large clinical trials, which would provide insight into clinical relevance of PGSs.38,56,57,58,59,60 Further, treating research participant cellular models (e.g., stem cell–derived organoids) with the relevant drugs, as described for the validation of a DILI PGS,44 would provide much needed functional validation for pharmacogenomic PGSs.

**CONCLUSIONS AND IMPACT OF SYSTEMATIC REVIEW**

We performed the first systematic review of the use of PGSs in pharmacogenomics to critically examine current strategies that are being used to apply PGSs to the field of pharmacogenomics. While the majority of studies examined the use of PGSs in the context of the treatment of mental health disorders, very little research has been performed in other areas of pharmacogenomics. Several limitations in current research were uncovered through our review of the literature. These include Eurocentric biases, poor adherence to PGS reporting guidelines and gaps in data availability and transparency. Based on these findings, we strongly recommend that future research in this area focuses on the development
of large globally representative pharmacogenomic consortia and that publications resulting from this research adhere to PRS-RS guidelines. As this field of research continues to grow, we believe that there are many promising applications for the use of PGSS in the context of pharmacogenomics and precision medicine to further improve treatment outcomes.

SUPPORTING INFORMATION
Supplementary information accompanies this paper on the Clinical Pharmacology & Therapeutics website (www.cpt-journal.com).

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CONFLICT OF INTEREST
The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
All authors wrote the manuscript. B.I.D., D.J., K.K., A.J., and G.E.B.W. designed the research. B.I.D., D.J., M.A.P.W., and S.M.L. performed the research. B.I.D., D.J., M.A.P.W., and S.M.L. analyzed the research.

DATA AVAILABILITY STATEMENT
The code used in this manuscript is available at https://github.com/Brittdrog/pgx_pgs_systematic_review.

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