## Pharmacogenomics and Health Disparities: a Systematic Literature Review

**Short running title:** Pharmacogenomics and health disparities: review

**Authors:** Antony Paul Martin, MSc1, Jennifer Downing, MA, PhD1, Michelle Maden, MA, FHEA3 Nigel Fleeman, MPH3, Ana Alfirevic, MD, PhD1, Alan Haycox, MA, PhD2,Munir Pirmohamed, MD, PhD1

**Institutions:** (1) Wolfson Centre for Personalised Medicine, University of Liverpool (2)Liverpool Health Economics, University of Liverpool Management School (3) Liverpool Reviews & Implementation Group, University of Liverpool

**Correspondence:**

Antony P. Martin

Wolfson Centre for Personalised Medicine

Department of Molecular & Clinical Pharmacology

University of Liverpool, Block A: Waterhouse Buildings,

1–5 Brownlow Street, Liverpool, L69 3GL

0151 795 3612

apmartin@liv.ac.uk

**Individual Author Contributions:** AM, MM, AA, JD, NF, AH and MP were involved with the conception and design of the study. AM, MM and JD were involved with acquisition of data. AM and JD were responsible for analysis and interpretation of data. All authors contributed to drafting the article, revising it critically for important intellectual content and had final approval of the version to be published.

**Ethical approval:** Not needed

**Word Count:** 3684 excluding title page, abstract, references, tables, and figure legends. (Abstract 198 Words)

## ABSTRACT

**Purpose:** This review assessed evidence of disparities in benefits of pharmacogenomics related to ‘model performance’ in subgroups of patients and studies which reported impact on health inequalities. ‘Model performance’ refers to the ability of algorithms including clinical, environmental and genetic information to guide treatment.

**Method:** A total of 4978 abstracts were screened by one reviewer and 30% (1494) were double screened by a second independent reviewer, after which data extraction was performed. Additional forward and backward citation searching of reference lists was conducted. Investigators independently double rated study quality and applicability of included studies.

**Results:** Onlyfiveindividual studies were identified which met our inclusion criteria, but were contradictory in their conclusions. While three studies of genotype-guided dosing of warfarin reported that ethnic disparities in health care may widen, two other studies (one on warfarin and on clopidogrel) suggested that disparities in health care may reduce. .

**Conclusion:** There is a paucity of studies which evaluate the impact of pharmacogenomics on health disparities. Further work is required not only to evaluate health disparities between ethnic groups and countries but also within ethnic groups in the same country, and solutions need to be identified to overcome these disparities.

**Key Words:** pharmacogenomics; genetics; efficacy; equity; disparities

**Registration:** Systematic review protocol was registered with PROSPERO, identification number: CRD42016032517

## INTRODUCTION

Minimizing modifiable health disparities is deemed fundamental for equitable and progressive achievement of universal health coverage.1 Equity refers to social justice or fairness; it is an ethical concept which is based on the principles of distributive justice.2 Equity in health can largely be defined as the absence of systematic disparities in health between social groups who have different levels of underlying social advantage, or different positions in social hierarchy.2 Equity in healthcare relates service provision to need, and therefore equity which focuses resources on those in greatest need is inherently just. Inequities in health systematically put people who may already be socially disadvantaged at further disadvantage in terms of health, and thus the term 'inequity' has a moral and ethical dimension.2 Inequity refers to differences which are unnecessary and avoidable but, in addition these differences may also be considered unfair and unjust.1,2

Precision medicine (PM) has the potential to revolutionize the health sector through improving the effectiveness of treatments whilst simultaneously reducing adverse effects and avoiding inappropriate treatment.3 PM tailors care for each individual patient based on clinical, environmental, and genetic information.3 In PM, the use of biomarkers (which to date have been mainly molecular) can be used for the purpose of risk assessment, diagnosis, prognosis, monitoring and guiding therapeutic decisions.3 Perhaps the most advanced area of PM is pharmacogenomics, which aims to relate genetic differences in the way drugs are handled (pharmacokinetic determinants) and how they act (pharmacodynamics determinants) to the differences in drug efficacy and safety observed between different individuals.4

Concerns have been raised by the European Personalized Medicine Association (EPEMED) and National Institute on Minority Health and Disparities (NIMHD) amongst others that the rate at which PM is implemented may vary. In particular new therapies or tests may be taken up less quickly and in lower numbers in more deprived populations due to challenges in access, availability and ability to pay privately and understanding of health care information compared to more educated and wealthier populations.3,5 In order to address this, as part of the US Precision Medicine Initiative (PMI), the *All of Us* research program aims to reflect the diversity of the U.S. population from varied social, racial/ethnic, and ancestral populations living in a variety of geographies, social environments, economic circumstances, age groups and health statuses.5

Several barriers exist in the delivery of PM, as described in Figure 1. Barriers to seeing a provider may occur due to differential awareness of personal risk, inability to attend appointments due to time constraints, sociodemographic factors and psychosocial factors.6 Sociodemographic factors include education level, socioeconomic status, marital status, age, sex, ethnicity and parenthood. Psychosocial factors include interest in PM, disease-specific stress, perceived risk, knowledge, perceived benefits, perceived limitations, anxiety, depression and general distress. Additional barriers include accessibility to providers with appropriate expertise and available resources.6

The remit of this review was to systematically review published evidence which considers whether PM interventions either widen or reduce health disparities.7 Given that PM as an overall area is relatively broad, we have focused the scope of the review on pharmacogenomics. Specifically, our research question examines barriers in effectiveness of pharmacogenomics related to ‘model performance’ in subgroups of patients. ‘Model performance’ refers to the ability of algorithms including clinical, environmental and genetic information to guide treatment. Our review also aims to identify studies which assessed the ‘effectiveness of pharmacogenomic interventions’ in subgroups of patients and reported impact on disparities in health care. These two factors are highlighted in Figure 1.

## METHODS

The systematic review protocol was registered with PROSPERO, the international database of prospectively registered systematic reviews (identification number CRD42016032517), conducted according to the Centre for Reviews and Dissemination’s guidance for undertaking reviews in healthcare and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis with a focus on health equity (PRISMA-E) guidelines.8,9

The scope of the research question was informed by the Campbell and Cochrane Equity Methods Group and the Cochrane Public Health Group who recommend the PROGRESS-Plus approach to analyses of health inequality information. PROGRESS-Plus is an acronym for place of residence, race/ethnicity, culture/language, occupation, gender/sex, religion, socioeconomic status and social capital and “Plus” captures other characteristics which may indicate a disadvantage, such as age and disability.7 This approach summarizes a number of social stratification factors understood to influence health opportunities, including the chance to participate and benefit from PM (see **Supplementary Table S1** online for definition of PROGRESS-Plus factors).

### Data Sources and Searches

The website of PharmGKB was searched to identify a total of 201 drugs that had labels containing pharmacogenetic information with differing approvals between European Medicines Agency (EMA), US Food and Drug Administration (FDA), Pharmaceuticals and Medical Device Agency, Japan (PMDA) and Health Canada, Santé Canada (HCSC).10 The types of regulatory recommendations provided were split into informative pharmacogenetic test (PGx), actionable PGx, genetic testing recommended, and genetic testing required.

We searched the following databases (via Ovid) between January 2006 and January 2016: Embase, MEDLINE, PubMed, The Cochrane Library and Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science. The search terms consisted of two clauses combined with the Boolean ‘AND’ operator. These pertained to a list of drugs identified from the PharmGKB website and health disparity terms. The search was restricted to studies of human subjects and written in the English language. Further articles were identified from searching the grey literature and backward citation searching of the reference lists of included studies and from forward citation searching using google scholar. The full search strategy is detailed in **Supplementary Table S2** online.

### Study Selection

Studies published over the past 10 years were reviewed to assess the most relevant evidence. Randomized controlled trials (RCTs), prospective and retrospective cohort studies, case-control studies and cross-sectional studies were included if they considered the impact of pharmacogenomic interventions on health disparities. It has been recommended that a wider array of evidence is included in reviews (such as non-randomized studies) as systematic reviews which have a focus on health equity may fail to identify assessments of effects on health equity due to strict inclusion criteria.7 However, we excluded editorials, letters, historical articles, reviews and abstracts.

We included English-language studies only because no evidence of a systematic bias exists from the use of English-language restrictions in systematic review-based meta-analyses in conventional medicine.11 We included studies on persons aged 16 years and above that measured outcomes directly and indirectly (e.g. self-reported). Studies that focused on genotyping to guide efficacy and discussed health equity issues were included. Studies were included if terms relating to impact on health disparities were stated in the title, abstract or keywords of the publication. Studies which discussed equity issues related to uptake rates associated with sociodemographic and psychosocial factors were outside the scope of this review (further information about our inclusion criteria is provided in **Supplementary Table S3** online).

### Screening, Data Extraction and Quality Assessment

Titles and abstracts were screened by one reviewer (AM) and 30% were double screened by a second independent reviewer (JD). Full texts were retrieved where reviewers were in agreement that the article met the inclusion criteria (99.4% agreement) and consensus was reached by discussion between the two reviewers. After determining article inclusion, one reviewer entered study data into evidence tables (AM); a second senior reviewer checked the information for accuracy and completeness (JD).

Data were extracted on the following study characteristics: year of publication, setting, study type, sample population, genetic test and health equity comment. We classified the included studies based on PROGRESS-Plus items (see **Supplementary Table S2** online for PROGRESS-Plus definitions of measures).21

AM graded the strength of the evidence using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE), quality assessment method (see **Supplementary Table S4** online). There were four categories of quality ratings in GRADE – ‘high’, ‘moderate’, ‘low’ and ‘very low’. Briefly, the default quality rating was ‘high’ for evidence from randomized controlled (including cluster) trials and ‘low’ for evidence from observational studies. Evidence for each study was examined for risks of bias, inconsistency, indirectness, imprecision and publication bias. Quality may be rated down if there is evidence of any of these five factors; for example, an observational study where risk of bias is judged to be serious would be rated down by 1 point from ‘low’ to ‘very low’. Alternatively, quality may be modified upward if there is a large magnitude of effect or if any plausible confounders were likely to minimize the observed effect. The quality of reporting of individual studies was expanded further in the narrative and additional information on how ratings were determined for each study was provided.12

### Data Synthesis and Analysis

Results are presented as summaries of individual studies and reported in the context of the impact of pharmacogenomics on health disparities. An overview of study quality using the GRADE method and equity considerations is provided. Evidence of equity impact was classified as:

* pro-equity (symbol: +) which refers to reduction in health disparities compared with the general population,
* anti-equity (symbol: -) which refers to an increase in health disparities, and
* mixed equity (symbol: ?) which refers to some improvement in an outcome for a vulnerable group but health disparities still persist and increase in other areas.

## RESULTS

### Study Selection and Characteristics

A total of 4978 papers were identified by the search of electronic databases. We retrieved 80 full-text articles, of which four met the inclusion criteria for the review and one additional article was identified from a hand search of reference lists and therefore five studies which met the inclusion criteria.13–17 Reasons for exclusion are presented in Figure 2. The heterogeneity in outcomes, methodologies and settings precluded meta-analysis.

The characteristics of the included studies are presented in Table 1. Of studies that were identified: four studies were based on evaluating genotype-guided dosing of warfarin to provide predictive information on anticoagulation response,13–16 while the fifth focused on the use of genotyping to guide treatment of the antiplatelet drug clopidogrel.17 No other drug-gene studies met our inclusion criteria.

Our final included studies were comprised of two from the USA,13,14 two studies from New Zealand15,17 and one study from Singapore.16 Of the included studies, four were prospective cohort studies13–16 and one study by Panattoni et al.17 was a cost-effectiveness analysis. The quality of reporting is shown in Table 1 according to the GRADE criteria. Initially, four of the studies13–16 were rated up due to consistent identification of association between cytochrome P450 (CYP) 2C9 (CYP2C9) enzyme and vitamin K epoxide reductase complex 1 (VKORC1) gene and warfarin dose requirements to achieve anticoagulation control. While, the fifth study17 was rated up due to consistent identification of association between CYP2C19 enzyme and metabolism rates of clopidogrel. There was limited risk of bias due to study design, importance of recruitment setting, presence of self-reported information and response rate. However, of the five studies, two studies15,17 were subsequently rated down due to use of prediction modelling simulation and possible indirectness issues. Both indirectness (e.g. comparators used) and imprecision (e.g. due to inaccuracies in measurement) were not substantial concerns for other included studies. Overall, three studies were deemed to be of ‘moderate quality’13,14,16 and the remaining two studies were deemed of ‘low quality’15,17.

Of five studies identified, three studies of genotype-guided dosing of warfarin reported that ethnic disparities in health care may widen.13,14,16 In contrast, one study of genotype-guided dosing of warfarin and one study of genotype-guided anti-platelet therapy reported that ethnic disparities in health care may reduce.15,17 In all five studies, the impact on disparities in health care was discussed but none of the studies quantified the resulting predicted increase or reduction in disparities in health care.

### Predicted impact of genotype-guided dosing of warfarin and health disparities

A study by Gladding et al.15 reported that genotype-guided dosing of warfarin could theoretically reduce ethnic health disparities as personalizing treatment using pharmacogenetics enables improved treatment by addressing underlying genetic differences between individuals. The study tested the frequency of known important variants within the VKORC1 (1639G/A) and CYP2C9 (\*2 and \*3) genes in a population of cardiac patients and then performed a simulation, based on genetic and personal factors, to estimate the mean dose of warfarin for different South Pacific ethnic groups.15 The authors report that while genetic variability within an ethnic group can be greater than between ethnic groups, no data existed for dose requirements in populations of Maori or Pacific Islander in New Zealand, nor have these groups been studied extensively in terms of pharmacogenetics. Gladding and colleagues highlight the importance of trial participation and long-term data collection for potentially under-served groups.15 Moreover, lack of trial participation and data collection can lead to mistreatment for understudied groups and therefore the potential treatment benefits may not be fully generalizable.18

In studies by Kealey et al.,13 Limdi et al.14 and Chan et al.16 the authors highlighted inconsistencies in the ability to provide predictive information for anticoagulation response with genotype-guided dosing of warfarin for certain ethnic groups compared to Caucasians. Moreover, these studies reported that health disparities widen due to poor characterization of genetic variants for certain groups of patients. Kealey et al. reported that at the time, no studies had been completed to evaluate whether genetic variation in CYP2C9 was useful in predicting warfarin response in African-Americans.13 A later study by Limdi et al.14 found that CYP2C9 and VKORC1 accounted for up to 30% of the variability in warfarin dose among European-Americans and 10% among African-Americans. Limdi and colleagues concluded that although CYP2C9 and VKORC1 genotyping has the potential to facilitate the development of individually tailored warfarin dose in both African-Americans and European-Americans, the ability to predict over-anticoagulation risk was limited to European-Americans.14 A further study by Chan et al.16 also found that there are different dose requirements between different races and there was considerable overlap in dose distributions depending on genotype combinations. Chan and colleagues revealed that genotype-guided dosing of warfarin can reduce inaccurate dosing by 18-24% in white individuals, whereas black, Japanese and Chinese individuals were not found to benefit from genotype-guided dosing of warfarin over standard dosing algorithms.16

### Genotype-guided treatment compared with treatment of clopidogrel or prasugrel alone and health disparities

A clinical trial found that patients with acute coronary syndromes (ACS) and reduced function allele CYP2C19\*2 (\*2 allele) who are treated with thienopyridines (anti-platelet medications), have an increased risk of adverse cardiac events with clopidogrel, but not prasugrel because prasugrel activation is not predominantly dependent on oxidation by the enzyme CYP2C19. A study by Panattoni et al.17 found that genotype-guided treatment compared with standard treatment of clopidogrel is a potentially cost-effective strategy for the entire New Zealand population and in particular for Maoris and Pacific Islander patients. It was reported that Maori and Pacific Islander ethnicities have a relatively high incidence of CYP2C19\*2 allele and therefore poor metabolizers of clopidogrel were more commonly identified. Increased cost-effectiveness was found in Maori and Pacific Islander ethnicities due to enhanced efficacy.19 Therefore, the authors concluded that the introduction of genotype-guided clopidogrel dosing has the potential to reduce ethnic disparities in health care as a result of enhanced treatment efficacy within a disadvantaged population group.17

## DISCUSSION

Our review to explore the impact of differing treatment responses on disparities in health care has highlighted a paucity of evidence with only 5 studies identified. The data that were available centered on differing pharmacogenomic treatment responses in different ethnic groups and how this may lead to disparities in health care. The case-studies of genotype-guided dosing of warfarin and genotype guided treatment of clopidogrel revealed several barriers which need to be overcome in order to fully realize potential treatment benefits.18 Most striking from our analysis is that no papers were identified which determined whether there were health disparities in the same ethnic group within the same country. Inequalities in health are determined by many different factors including socioeconomic, and more work will be needed in this area as precision medicine approaches become implemented into practice.

Research on the impact of pharmacogenomics on disparities in health care may have been hindered by the relative lack of implementation into clinical practice due to associated lack of cost effectiveness evidence. A systematic review found robust evidence of cost-effectiveness for pharmacogenomic testing for prevention of adverse drug reactions only for a limited number of drugs (abacavir, allopurinol, carbamazepine, clopidogrel and irinotecan) even though over 200 drugs were identified with labels containing pharmacogenetic information.20

Warfarin has a narrow therapeutic index and thus getting the dose correct is crucial to prevent either excessive or insufficient anticoagulation.21,22 It was estimated in the US that hospital admissions related to warfarin complications were estimated to cost on average US$10 819 per patient and that the cost of drug-related morbidity and mortality exceeded US$177 billion.23 Recently the results of two large RCTs which evaluated genotype-guided dosing of warfarin were published, one which was conducted in Europe (EU-PACT)21 and the other in the USA (COAG).22 EU-PACT demonstrated that genotype-guided dosing compared to fixed loading dose regimen in newly diagnosed patients with thromboembolic disorder in the UK and Sweden found an improved achievement of the primary outcome of percentage time within target INR (TTR) evaluated over 3 months.21 COAG failed to show an improvement in TTR compared to a clinical algorithm.22 African-American patients in COAG were less likely to achieve TTR in the genotyped arm compared with the control arm22 While EU-PACT consisted of an ethnically homogenous cohort (97% white), COAG was an ethnically heterogeneous cohort (67% white, 27% black, 6% Hispanic). CYP2C9 \*2 and \*3 allele frequencies are lower in African Americans than European Americans (1% and 2%, respectively and 6% and 10%, respectively), while other SNPs are present in African Americans but are rare in Caucasians (CYP2C9\*8 and \*11). The latter SNPs however were not assessed to inform dosing African American patients in COAG.21,22 A cost-effectiveness analysis of the EU-PACT trial showed that genotype-guided dosing in the UK and Swedish populations was cost-effective when compared with current standard clinical care.24 It is now clear that ethnicity-stratified analysis can improve dose prediction across ethnic groups when compared to ethnicity-combined analysis.25 Such population-specific warfarin pharmacogenomic dosing algorithms are likely to address, at least in part, a source of health disparities in pharmacogenetically under-served groups.25–27

Clopidogrel is a commonly prescribed antiplatelet drug. Clopidogrel is a prodrug which is metabolized by CYP2C19 to become active. While patients with reduced-function variants (\*2, \*3, \*4 and \*8) require higher doses of the drug, patients with a gain-of-function variant (\*17) require lower dose.28 Individuals may have a combination of variants and the Clinical Pharmacogenetics Implementation Consortium (CPIC) has developed guidelines for differing metabolism rates to inform treatment strategies.29 The prevalence of variants differs by ethnicity; the most common CYP2C19 loss-of-function (LOF) allele is \*2 with allele frequencies of 29-35% in Asians and only ~15% in Caucasians and Africans.29 The study by Panattoni et al19 highlights how variation in the frequency of the variant allele in certain ethnic populations can confer benefits in that population and potentially reduce health inequalities.

It is important to note that clopidogrel treatment failure is multi-factorial as non-compliance, drug-drug interactions and comorbidities may also have a clinically significant impact on health outcomes.30 Therefore to date, due to a lack of prospective data from RCTs which would adjust for confounding factors, genotyping to identify CYP2C19 LOF alleles is not yet widely recommended as part of routine clinical care.30 However, two large prospective RCTs (TAILOR-PCI and POPular Genetics study) are underway to address this gap in clinical evidence.30

From both pharmacogenomic examples, it is apparent that identifying genetic variants in genes across an ethnically diverse population can improve treatment algorithms to optimize care. A report by the PMI Working Group further explains that knowledge of genetic variability in different ethnic groups is necessary to identify variations in disease etiology and course.5 The results of this review identified a small number of studies which have focused on the impact of pharmacogenomics on health disparities. However, from our findings it is difficult to state with any degree of certainty as to whether health disparities have been widened or reduced by pharmacogenomics. Indeed, the results from this review should be treated with caution as ‘absence of evidence is not evidence of absence’.

Access to, and knowledge-based disparities in, implementation of pharmacogenomics in clinical practice may be compounded by a paucity of evidence of clinical effectiveness in underserved groups. Furthermore, provider and patient relations are paramount for the potential realization of PM. There is known substantial disparity in uptake of genetic tests, which has been found to be associated with a range of psychosocial, sociodemographic factors and clinical factors.6 Therefore, proactive initiatives to minimize and prevent disparities caused by these factors should be encouraged. This should include conscious decisions to ensure that there is participation across sociodemographic groups during the development phase to ensure that the potential benefits from pharmacogenomic research are fully realized.18,31

A limitation of the scope of this review is that impact on health disparities is rarely reported in primary clinical studies. Moreover, the electronic search may have failed to identify potential sources of evidence if terms relating to impact on health disparities were not stated in the title, abstract or keywords of the publication. Furthermore, none of the included studies attempted to quantify the impact of pharmacogenomic-guided treatment on health disparities.13–16,19 Despite these limitations it is important to emphasize again that we did not identify any studies that specifically evaluated health disparities caused by pharmacogenomics within the same ethnic group in the same country. A report by the WHO Commission on Social Determinants of Health (2008) highlighted the overarching importance of improving daily living conditions and combating the inequitable distribution of money, power and resources in reducing health disparities.32 While pharmacogenomics is not a main determinant for population health, since translation of research is at such an early stage, a proactive approach provides an opportunity to ensure future advancements benefit disadvantaged populations.

In summary, our review has highlighted that there is limited analysis and reporting of impact on health disparities in pharmacogenomics studies. In the literature, it is widely acknowledged that concerted efforts are required to ensure that the underserved and vulnerable populations also have future access to clinical innovations. However, whether this is happening is unclear at present, and thus future pharmacogenomics studies should incorporate equity assessments to address the existing gap in evidence.

## DISCLOSURE

This study was supported by the National Institute of Health Research Collaboration for Leadership in Applied Health Research and Care North West Coast (NIHR CLAHRC NWC). The investigators were solely responsible for the content and the decision to submit the manuscript for publication. The funding source had no role in the selection, critical appraisal, or synthesis of evidence. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

## REFERENCES

1. Hosseinpoor AR, Bergen N, Koller T, et al. Equity-Oriented Monitoring in the Context of Universal Health Coverage. *PLoS Med*. 2014;11(9):e1001727. doi:10.1371/journal.pmed.1001727.

2. Whitehead M. The concepts and principles of equity and health. *Health Promot Int*. 1991;6(3):217-228. doi:10.1093/heapro/6.3.217.

3. EPEMED. *Personalized Medicine in Europe – Enhancing Patient Access to Pharmaceutical Companion Products*.; 2014.

4. Shargel L, Wu-Pong S, ABC Y. Applied biopharmaceutics and pharmacokinetics. In: 5th ed. New York: McGraw-Hill; 2005:258-267.

5. NIH. Precision Medicine Initiative Cohort Program. https://www.nih.gov/precision-medicine-initiative-cohort-program. Published 2016. Accessed September 23, 2016.

6. Sweeny K, Ghane A, Legg AM, Huynh HP, Andrews SE. Predictors of genetic testing decisions: A systematic review and critique of the literature. *J Genet Couns*. 2014;23(3):263-288. doi:10.1007/s10897-014-9712-9.

7. Welch V a, Petticrew M, O’Neill J, et al. Health equity: evidence synthesis and knowledge translation methods. *Syst Rev*. 2013;2(1):43. doi:10.1186/2046-4053-2-43.

8. CRD. *Systematic Reviews: CRD’s Guidance for Undertaking Reviews in Health Care*. doi:10.1016/S1473-3099(10)70065-7.

9. Welch V, Petticrew M, Tugwell P, et al. PRISMA-Equity 2012 Extension: Reporting Guidelines for Systematic Reviews with a Focus on Health Equity. *PLoS Med*. 2012;9(10):1-2. doi:10.1371/journal.pmed.1001333.

10. PharmGKB. Drug Labels. https://www.pharmgkb.org/view/drug-labels.do. Published 2015. Accessed December 28, 2016.

11. Morrison A, Polisena J, Husereau D, et al. The Effect of English-Language Restriction on Systematic Review-Based Meta-Analyses: a Systematic Review of Empirical Studies. *Int J Technol Assess Health Care*. 2012;28(2):138-144. doi:10.1017/S0266462312000086.

12. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394. doi:10.1016/j.jclinepi.2010.04.026.

13. Kealey C, Chen Z, Christie J, et al. Warafin and cytochrome P450 2C9 genotype: Possible ethic variation in warafin sensitivity. *Pharmacogenomics*. 2007;8(3):217-225. doi:10.2217/14622416.8.3.217.

14. Limdi NA, Arnett DK, Goldstein JA, et al. Influence of CYP2C9 and VKORC1 on warfarin dose, anticoagulation attainment and maintenance among European-Americans and African-Americans. *Pharmacogenomics*. 2008;9(5):511-526. doi:10.2217/14622416.9.5.511.

15. Gladding P, Stewart R, Webster M, White H. A Simulation of Warfarin Maintenance Dose Requirement Using a Pharmacogenomic Algorithm in an Ethnically Diverse Cohort. *Hear Lung Circ*. 2009;18:S11. doi:10.1016/j.hlc.2009.04.026.

16. Chan SL, Suo C, Chia KS, Teo YY. The population attributable fraction as a measure of the impact of warfarin pharmacogenetic testing. *Pharmacogenomics*. 2012;13(11):1247-1256. doi:10.2217/pgs.12.104.

17. Panattoni L, Brown PM, Ao B Te, Webster M, Gladding P. The cost effectiveness of genetic testing for CYP2C19 Variants to Guide Thienopyridine Treatment in Patients with Acute Coronary Syndromes: A New Zealand Evaluation. *Pharmacoeconomics*. 2012;30(11):1067-1084. doi:10.2165/11595080-000000000-00000.

18. Manrai AK, Funke BH, Rehm HL, et al. Genetic Misdiagnoses and the Potential for Health Disparities. *N Engl J Med*. 2016;375(7):655-665. doi:10.1056/NEJMsa1507092.

19. Panattoni L, Brown PM, Ao B Te, Webster M, Gladding P. The cost effectiveness of genetic testing for CYP2C19 Variants to Guide Thienopyridine Treatment in Patients with Acute Coronary Syndromes: A New Zealand Evaluation. *Pharmacoeconomics*. 2012;30(11):1067-1084. doi:10.2165/11595080-000000000-00000.

20. Plumpton CO, Roberts D, Pirmohamed M, Hughes DA. A Systematic Review of Economic Evaluations of Pharmacogenetic Testing for Prevention of Adverse Drug Reactions. *Pharmacoeconomics*. 2016. doi:10.1007/s40273-016-0397-9.

21. Anderson JL, Gage BF, Rosenberg YD, et al. A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosin. *N Engl J Med*. 2013;369(24):2283-2293. doi:10.1056/NEJMoa1310669.

22. Kimmel SE, French BF, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med*. 2013;369(24):2283-2293. doi:10.1056/NEJMoa1310669.

23. Finlayson a E, Godman B, Paterson K, et al. Personalizing healthcare: from genetics through payment to improving care? *J R Soc Med*. 2013;106(2):41-44. doi:10.1258/jrsm.2012.120193.

24. Verhoef TI, Redekop WK, Langenskiold S, et al. Cost-effectiveness of pharmacogenetic-guided dosing of warfarin in the United Kingdom and Sweden. *Pharmacogenomics J*. 2016;16(5):478-484. doi:10.1038/tpj.2016.41.

25. Perera MA, Cavallari LH, Limdi NA, et al. Genetic variants associated with warfarin dose in African- American individuals : a genome-wide association study. *Lancet*. 2013;382(9894):790-796. doi:10.1016/S0140-6736(13)60681-9.

26. Kubo K, Ohara M, Tachikawa M, et al. Population differences in S -warfarin pharmacokinetics among African Americans , Asians and whites : their in fl uence on pharmacogenetic dosing algorithms. *Pharmacogenomics J*. 2016;0:1-7. doi:10.1038/tpj.2016.57.

27. Daneshjou R, Gamazon ER, Burkley B, et al. Genetic variant in folate homeostasis is associated with lower warfarin dose in African Americans. *Blood*. 2014;124(14):2298-2306. doi:10.1182/blood-2014-04-568436.R.D.

28. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic Determinants of Response to Clopidogrel and Cardiovascular Events. *N Engl J Med*. 2009;360(4):363-375.

29. Scott SA, Sangkuhl K, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C19 Genotype and Clopidogrel Therapy : 2013 Update. *Clin Pharmacol Ther*. 2013;94(3):317-323. doi:10.1038/clpt.2013.105.

30. Pereira NL, Geske JB, Mayr M, Shah SH, Rihal CS. Pharmacogenetics of clopidogrel. *Circ Cardiovasc Genet*. 2016;9(2):185-188. doi:10.1161/CIRCGENETICS.115.001318.

31. Tan DSW, Mok TSK, Rebbeck TR. Cancer genomics: Diversity and disparity across ethnicity and geography. *J Clin Oncol*. 2016;34(1):91-101. doi:10.1200/JCO.2015.62.0096.

32. World Health Organization. *Closing the Gap in a Generation*.; 2008. doi:10.1080/17441692.2010.514617.

## FIGURES

Figure 1 Barriers to the delivery of pharmacogenomic interventions

Figure 2 PRISMA flow diagram displaying articles included and excluded in this review



Table 1 Summary of included studies

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Reference | N | Test type | Average age | Age Range or SD | % Women | Description of sample | Country | Equity comment |  | GRADE |
| Kealey et al (2007)13 | T=362; C=194; AA=168 | CYP2C9 (\*2 and \*3) and VKORC (11173 C/T) genotype | 58.7 | 45-72 | 30.9 | A prospective cohort of patients (of various indications) with a target international normalized ratio of between 2.0 and 3.0 were genotyped | USA | Uncertain usefulness of variants in African-Americans to provide predictive information in anticoagulation response | Ethnicity -  | 3 |
| Limdi et al (2008)14 | T=575; EA=302; AA=273 | CYP2C9 (\*2, \*3, \*5, \*6 and \*11) and VKORC1 (1173C/T, 3730G/A, 2255C/T, 1542G/C) genotype | 61.1 | SD +14.7-16.0 | 48.7 | A prospective cohort of patients (of various indications) with a target international normalized ratio of between 2.0 and 3.0 were genotyped  | USA | Inconsistent ability to provide predictive information in anticoagulation response | Ethnicity -  | 3 |
| Gladding et al (2009)15 | T=366; M=49; PI=21; CH=9 | CYP2C9 (\*2 and \*3) and VKORC1 (1639G/A) genotype | 68.6 | SD +9-12 | - | A prospective cross-sectional simulation study of patients with severe coronary disease  | New Zealand | Study guides warfarin maintenance dose and therefore may reduce ethnic disparities in treatment outcomes | Ethnicity + | 2 |
| Chan et al (2012)16 | T=3672; W=2543; B=639; J=227; CH=263 | CYP2C9 (\*2 and \*3) and VKORC1 (1639AA) genotype | -  | - | - | Patients included in IWPC dataset from 22 study sites with a target international normalized ratio of between 2.0 and 3.0  | Singapore | Warfarin PGx testing reduces inaccurate dosing in white patients but black, Japanese and Chinese do not benefit | Ethnicity -  | 3 |
| Panattoni et al (2012)17 | T=13608; E=-; M=-; ETA=-; PI=- | CYP2C19 (\*2) genotype | - | 45-80 | - | Cost-effectiveness analysis using international multicentre RCT data of genetic testing for CYP2C19 variants to guide thienopyridine treatment patients with ACS  | New Zealand | Treatment strategy has potential to reduce ethnic health disparities | Ethnicity +  | 2 |

Acronyms: CYP2C9 = cytochrome P450 (CYP)2C9 enzyme; CYP2C19 = cytochrome P450 (CYP)2C19 enzyme; VKORC1 = vitamin K epoxide reductase enzyme; PGx = pharmacogenetic test; ACS = acute coronary syndrome; IWPC = International Warfarin Pharmacogenetics Consortium; SD = standard deviation; T = total; C = Caucasian; AA = African American; EA = European American; M =Mãori; PI = Pacific Islander; CH = Chinese; W = White; B = Black; J =Japanese; E = European; ETA = East Asian

## Appendix

Supplementary Table S1 Definitions of PROGRESS-Plus factors

|  |  |
| --- | --- |
| **PROGESS** | **Definition** |
| Place of residence | Rural/urban, country/state, area deprivation, housing characteristics |
| Ethnicity\* | Ethnic background |
| Occupation | Professional, skilled, unskilled, unemployed etc. |
| Gender\* | Male or female |
| Religion | Religious background |
| Education\* | Years in and/or level of education attained, school type |
| Social capital | Neighborhood/community/family support |
| Socio-economic position\* (SEP/income) | Income-related measure e.g. means-tested benefits/welfare, affluence |
| **Plus** | **Definition** |
| All SEP | SEP income related, plus occupation, education, and elementsof place of residence |
| Age\* | Age range |
| Disability | Existence of physical or emotional/mental disability |
| Sexual orientation | Heterosexual, gay, lesbian, bisexual, transgender  |
| Other vulnerable groups | School non-attenders, looked after young person (YP), YP in criminal justicesystem, victims of abuse, runaways, teenage parents |

\* Included measures within this table which data was sought and extracted.

Supplementary Table S2 Search strategy

|  |  |  |
| --- | --- | --- |
| Search Number, by Date and Database | Search Terms | Articles Returned, n |
| **January 2016EMBASE**  |  |
| 1 | ((((((health adj2 inequalit\*) or health) adj2 equit\*) or health) adj2 inequit\*) or (social gradient\* adj3 (reduc\* or difference\* or disparit\* or increase\* or inequit\* or inequalit\* or equit\* or disadvantage\*))).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 1483 |
| 2 | (gender-based or gender-related or gender differences or gender factors).mp.  | 33483 |
| 3 | ((sex or gender) adj2 (analysis or specific or difference? or factor? or inequit$ or disparit$ or inequalit$)).mp. | 359995 |
| 4 | ((ethnic$ or race or racial or religio$ or cultur$ or minorit$ or refugee or indigenous or aboriginal) adj3 (analysis or difference$ or specific or disparit$ or inequalit$ or inequit$)).mp. | 105055 |
| 5 | exp geriatrics/  | 45976 |
| 6 | exp homosexuality/  | 218191 |
| 7 | exp disabled person/  | 27930 |
| 8 | ((poverty or low-income or socioeconomic$ or social) adj2 (analysis or disadvantage$ or specific or difference? or factor? or inequalit$ or depriv$ or inequit$ or disparit$)).mp.  | 40646 |
| 9 | exp educational status/  | 48514 |
| 10 | exp socioeconomics/  | 201417 |
| 11 | ((discriminat$ or social exclu$ or social inclu$) adj3 (religion or culture or race or racial or aboriginal or indigenous or ethnic$)).mp.  | 1322 |
| 12 | ((urban or rural or inner-city or slum) adj2 (difference$ or specific or analysis or inequit$ or disparit$ or inequalit$)).mp.  | 7056 |
| 13 | ((resource-poor or (low-income adj countr$) or (middle income adj countr$) or africa or developing countr$ or south america or china or asia or latin america) adj2 (relevance or analysis or specific or difference or applicab$ or inequit$ or disparit$ or inequalit$)).mp.  | 1843 |
| 14 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13  | 746064 |
| 15 | exp personalized medicine/  | 15782 |
| 16 | ((Abacavir or abiraterone or acetaminophen or afatinib or afutuzumab or aliskiren or amitriptyline or anastrozole or arformoterol or aripiprazole or arsenic trioxide or atazanavir or atomoxetine or atorvastatin or axitinib or azathioprine) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 400 |
| 17 | ((Belimumab or boceprevir or bosutinib or brentuximab vedotin or busulfan) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 57 |
| 18 | ((Cabazitaxel or capecitabine or carbamazepine or carglumic acid or carisoprodol or carvedilol or celecoxib or ceritinib or cetuximab or cevimeline or chloroquine or chlorpropamide or cisplatin or citalopram or clobazam or clomifene or clomipramine or clopidogrel or clozapine or codeine or crizotinib) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] | 1258 |
| 19 | ((Dabrafenib or dapsone or darifenacin or darunavir or dasatinib or denileukin diftitox or desflurane or desipramine or desloratadine or dexlansoprazole or dextromethorphan or diazepam or divalproex sodium or doxepin or dronedarone or drospirenone) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 161 |
| 20 | ((Efavirenz or eliglustat or eltrombopag or emtricitabine or erlotinib or erythromycin or esomeprazole or ethinyl or estradiol or everolimus or exemestane) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 744 |
| 21 | ((Fampridine or fesoterodine or fluorouracil or fluoxetine or flurbiprofen or fluvoxamine or fosamprenavir or fulvestrant) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 291 |
| 22 | ((Galantamine or gefitinib or glibenclamide or glimepiride or glipizide) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 127 |
| 23 | ((Homoharringtonine or hydralazine) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 10 |
| 24 | ((ibritumomab or ibrutinib or iloperidone or imatinib or imipramine or indacaterol or indinavir or irinotecan or isoflurane or isoniazid or isosorbide dinitrate or ivabradine or ivacaftor) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 507 |
| 25 | ((lansoprazole or lapatinib or lenalidomide or letrozole or lomitapide) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 86 |
| 26 | ((mafenide or maraviroc or mercaptopurine or methylene blue or metoclopramide or metoprolol or mipomersen or modafinil or mycophenolic acid) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 168 |
| 27 | ((nalidixic acid or nefazodone or nelfinavir or nilotinib or nitrofurantoin or norelgestromin or norfloxacin or nortriptyline) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 78 |
| 28 | ((ofatumumab or olanzapine or omeprazole) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 94 |
| 29 | ((panitumumab or pantoprazole or paroxetine or pazopanib or peginterferon alfa-2b or pegloticase or perphenazine or pertuzumab or phenylacetic acid or phenytoin or pimozide or ponatinib or posaconazole or prasugrel or pravastatin or primaquine or probenecid or propafenone or propranolol or protriptyline or pyrazinamide) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 344 |
| 30 | ((quinidine or quinine) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 32 |
| 31 | ((rabeprazole or ranolazine or rasburicase or regorafenib or rifampin or risperidone or ritonavir or rituximab or rosuvastatin or ruxolitinib) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 271 |
| 32 | ((Sevoflurane or sildenafil or simeprevir or sirolimus or sodium benzoate or sodium nitrite or sodium phenylbutyrate or sofosbuvir or succimer or succinylcholine or sulfadiazine or sulfamethoxazole or sulfasalazine or sulfisoxazole or sunitinib) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 172 |
| 33 | ((tamoxifen or telaprevir or telithromycin or tenofovir or terbinafine or tetrabenazine or thioguanine or thioridazine or ticagrelor or timolol or tiotropium or tipranavir or tolterodine or tositumomab or tramadol or trametinib or trastuzumab or trastuzumab emtansine or tretinoin or trimethoprim or trimipramine) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 570 |
| 34 | ((valproic acid or vandetanib or vardenafil or velaglucerase alfa or vemurafenib or venlafaxine or vitamin c or voriconazole or vortioxetine) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 156 |
| 35 | (warfarin adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 895 |
| 36 | (zonisamide adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] | 2 |
| 37 | ((personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*) adj5 (medicin\* or health\* or drug\*)).mp.  | 54384 |
| 38 | or/15-37  | 59761 |
| 39 | 14 and 38  | 3037 |
| 40 | limit 39 to (english language and yr="1999 - 2016") (**2649**) | 2649 |
|  |  |  |
| **January 2016MEDLINE (Ovid)**  |  |
| 1 | ((((((health adj2 inequalit\*) or health) adj2 equit\*) or health) adj2 inequit\*) or (social gradient\* adj3 (reduc\* or difference\* or disparit\* or increase\* or inequit\* or inequalit\* or equit\* or disadvantage\*))).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] | 1117 |
| 2 | (gender-based or gender-related or gender differences or gender factors).mp.  | 22298 |
| 3 | ((sex or gender) adj2 (analysis or specific or difference? or factor? or inequit$ or disparit$ or inequalit$)).mp.  | 276176 |
| 4 |  ((ethnic$ or race or racial or religio$ or cultur$ or minorit$ or refugee or indigenous or aboriginal) adj3 (analysis or difference$ or specific or disparit$ or inequalit$ or inequit$)).mp.  | 45975 |
| 5 | exp geriatrics/  | 27790 |
| 6 | exp homosexuality/ | 23970 |
| 7 | exp disabled person/  | 53716 |
| 8 | ((poverty or low-income or socioeconomic$ or social) adj2 (analysis or disadvantage$ or specific or difference? or factor? or inequalit$ or depriv$ or inequit$ or disparit$)).mp.  | 144892 |
| 9 | exp educational status/  | 42933 |
| 10 | exp economics/  | 519938 |
| 11 | ((discriminat$ or social exclu$ or social inclu$) adj3 (religion or culture or race or racial or aboriginal or indigenous or ethnic$)).mp.  | 1055 |
| 12 | ((urban or rural or inner-city or slum) adj2 (difference$ or specific or analysis or inequit$ or disparit$ or inequalit$)).mp.  | 2529 |
| 13 | ((resource-poor or (low-income adj countr$) or (middle income adj countr$) or africa or developing countr$ or south america or china or asia or latin america) adj2 (relevance or analysis or specific or difference or applicab$ or inequit$ or disparit$ or inequalit$)).mp.  | 1323 |
| 14 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13  | 1058614 |
| 15 | exp personalized medicine/  | 7250 |
| 16 | ((Abacavir or abiraterone or acetaminophen or afatinib or afutuzumab or aliskiren or amitriptyline or anastrozole or arformoterol or aripiprazole or arsenic trioxide or atazanavir or atomoxetine or atorvastatin or axitinib or azathioprine) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 198 |
| 17 | ((Belimumab or boceprevir or bosutinib or brentuximab vedotin or busulfan) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 26 |
| 18 |  ((Cabazitaxel or capecitabine or carbamazepine or carglumic acid or carisoprodol or carvedilol or celecoxib or ceritinib or cetuximab or cevimeline or chloroquine or chlorpropamide or cisplatin or citalopram or clobazam or clomifene or clomipramine or clopidogrel or clozapine or codeine or crizotinib) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 610 |
| 19 | ((Dabrafenib or dapsone or darifenacin or darunavir or dasatinib or denileukin diftitox or desflurane or desipramine or desloratadine or dexlansoprazole or dextromethorphan or diazepam or divalproex sodium or doxepin or dronedarone or drospirenone) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 100 |
| 20 | ((Efavirenz or eliglustat or eltrombopag or emtricitabine or erlotinib or erythromycin or esomeprazole or ethinyl or estradiol or everolimus or exemestane) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 656 |
| 21 | ((Fampridine or fesoterodine or fluorouracil or fluoxetine or flurbiprofen or fluvoxamine or fosamprenavir or fulvestrant) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 519 |
| 22 | ((Galantamine or gefitinib or glibenclamide or glimepiride or glipizide) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 24 |
| 23 | ((Homoharringtonine or hydralazine) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 12 |
| 24 | ((ibritumomab or ibrutinib or iloperidone or imatinib or imipramine or indacaterol or indinavir or irinotecan or isoflurane or isoniazid or isosorbide dinitrate or ivabradine or ivacaftor) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 289 |
| 25 |  ((lansoprazole or lapatinib or lenalidomide or letrozole or lomitapide) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 28 |
| 26 | ((mafenide or maraviroc or mercaptopurine or methylene blue or metoclopramide or metoprolol or mipomersen or modafinil or mycophenolic acid) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 120 |
| 27 | ((nalidixic acid or nefazodone or nelfinavir or nilotinib or nitrofurantoin or norelgestromin or norfloxacin or nortriptyline) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 69 |
| 28 | ((ofatumumab or olanzapine or omeprazole) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 63 |
| 29 | ((panitumumab or pantoprazole or paroxetine or pazopanib or peginterferon alfa-2b or pegloticase or perphenazine or pertuzumab or phenylacetic acid or phenytoin or pimozide or ponatinib or posaconazole or prasugrel or pravastatin or primaquine or probenecid or propafenone or propranolol or protriptyline or pyrazinamide) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 330 |
| 30 | ((quinidine or quinine) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 54 |
| 31 | ((rabeprazole or ranolazine or rasburicase or regorafenib or rifampin or risperidone or ritonavir or rituximab or rosuvastatin or ruxolitinib) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 287 |
| 32 | ((Sevoflurane or sildenafil or simeprevir or sirolimus or sodium benzoate or sodium nitrite or sodium phenylbutyrate or sofosbuvir or succimer or succinylcholine or sulfadiazine or sulfamethoxazole or sulfasalazine or sulfisoxazole or sunitinib) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 144 |
| 33 | ((tamoxifen or telaprevir or telithromycin or tenofovir or terbinafine or tetrabenazine or thioguanine or thioridazine or ticagrelor or timolol or tiotropium or tipranavir or tolterodine or tositumomab or tramadol or trametinib or trastuzumab or trastuzumab emtansine or tretinoin or trimethoprim or trimipramine) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 1689 |
| 34 | ((valproic acid or vandetanib or vardenafil or velaglucerase alfa or vemurafenib or venlafaxine or vitamin c or voriconazole or vortioxetine) adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 177 |
| 35 | (warfarin adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 568 |
| 36 | (zonisamide adj5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]  | 1 |
| 37 | ((personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*) adj5 (medicin\* or health\* or drug\*)).mp.  | 54384 |
| 38 | or/15-37  | 35595 |
| 39 | 14 and 38  | 2375 |
| 40 | limit 39 to (yr="1999 - 2016")  | 1898 |
|  |  |  |
| **January 2016PubMed (last 6 months)**  |  |
| 1 | ((health) AND (inequalit\* or equit\* or inequit\*)) OR ((social gradient\* and (reduc\* or difference\* or disparit\* or increase\* or inequit\* or inequalit\* or equit\* or disadvantage\*))  | 30275 |
| 2 | (gender-based or gender-related or gender differences or gender factors)  | 514025 |
| 3 | ((sex or gender) and (analysis or specific or difference\* or factor\* or inequit\* or disparit\* or inequalit\*))  | 279104 |
| 4 | ((ethnic\* or race or racial or religio\* or culture\* or minorit\* or refugee or indigenous or aboriginal) and (analysis or difference\* or specific or disparit\* or inequality\* or inequit\*))  | 883967 |
| 5 | geriatrics  | 51468 |
| 6 | homosexuality  | 24614 |
| 7 | disabled person  | 56052 |
| 8 | ((poverty or low-income or socioeconomic\* or social) and (analysis or disadvantage\* or specific or difference\* or factor\* or inequality\* or depriv\* or inequit\* or disparit\*))  | 478051 |
| 9 | educational status  | 58071 |
| 10 | socioeconomics  | 383399 |
| 11 | ((discriminat\* or social exclu\* or social inclu\*) and (religion or culture or race or racial or aboriginal or indigenous or ethnic\*))  | 11647 |
| 12 | ((urban or rural or inner-city or slum) and (difference\* or specific or analysis or inequit\* or disparit\* or inequality\*))  | 123326 |
| 13 | ((resource-poor or (low-income and countr\*) or (middle income and countr\*) or africa or developing countr\* or south america or china or asia or latin america) and (relevance or analysis or specific or difference or applicab\* or inequit\* or disparit\* or inequality\*))  | 840741 |
| 14 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13  | 2739648 |
| 15 | personalized medicine  | 27424 |
| 16 | ((Abacavir or abiraterone or acetaminophen or afatinib or afutuzumab or aliskiren or amitriptyline or anastrozole or arformoterol or aripiprazole or arsenic trioxide or atazanavir or atomoxetine or atorvastatin or axitinib or azathioprine) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 4026 |
| 17 | ((Belimumab or boceprevir or bosutinib or brentuximab vedotin or busulfan) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 576 |
| 18 | ((Cabazitaxel or capecitabine or carbamazepine or carglumic acid or carisoprodol or carvedilol or celecoxib or ceritinib or cetuximab or cevimeline or chloroquine or chlorpropamide or cisplatin or citalopram or clobazam or clomifene or clomipramine or clopidogrel or clozapine or codeine or crizotinib) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 12253 |
| 19 | ((Dabrafenib or dapsone or darifenacin or darunavir or dasatinib or denileukin diftitox or desflurane or desipramine or desloratadine or dexlansoprazole or dextromethorphan or diazepam or divalproex sodium or doxepin or dronedarone or drospirenone) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 3167 |
| 20 | ((Efavirenz or eliglustat or eltrombopag or emtricitabine or erlotinib or erythromycin or esomeprazole or ethinyl or estradiol or everolimus or exemestane) and ((personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 13270 |
| 21 | ((Fampridine or fesoterodine or fluorouracil or fluoxetine or flurbiprofen or fluvoxamine or fosamprenavir or fulvestrant) (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 5200 |
| 22 | ((Galantamine or gefitinib or glibenclamide or glimepiride or glipizide) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 1442 |
| 23 | ((Homoharringtonine or hydralazine) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 315 |
| 24 | ((ibritumomab or ibrutinib or iloperidone or imatinib or imipramine or indacaterol or indinavir or irinotecan or isoflurane or isoniazid or isosorbide dinitrate or ivabradine or ivacaftor) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 5584 |
| 25 | ((lansoprazole or lapatinib or lenalidomide or letrozole or lomitapide) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic)) | 938 |
| 26 | ((mafenide or maraviroc or mercaptopurine or methylene blue or metoclopramide or metoprolol or mipomersen or modafinil or mycophenolic acid) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic)) | 2508 |
| 27 | ((nalidixic acid or nefazodone or nelfinavir or nilotinib or nitrofurantoin or norelgestromin or norfloxacin or nortriptyline) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic)) | 2042 |
| 28 | ((ofatumumab or olanzapine or omeprazole) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 982 |
| 29 | ((panitumumab or pantoprazole or paroxetine or pazopanib or peginterferon alfa-2b or pegloticase or perphenazine or pertuzumab or phenylacetic acid or phenytoin or pimozide or ponatinib or posaconazole or prasugrel or pravastatin or primaquine or probenecid or propafenone or propranolol or protriptyline or pyrazinamide) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 4022 |
| 30 | ((quinidine or quinine) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic)) | 736 |
| 31 | ((rabeprazole or ranolazine or rasburicase or regorafenib or rifampin or risperidone or ritonavir or rituximab or rosuvastatin or ruxolitinib) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic)) | 4615 |
| 32 | ((Sevoflurane or sildenafil or simeprevir or sirolimus or sodium benzoate or sodium nitrite or sodium phenylbutyrate or sofosbuvir or succimer or succinylcholine or sulfadiazine or sulfamethoxazole or sulfasalazine or sulfisoxazole or sunitinib) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 4379 |
| 33 | ((tamoxifen or telaprevir or telithromycin or tenofovir or terbinafine or tetrabenazine or thioguanine or thioridazine or ticagrelor or timolol or tiotropium or tipranavir or tolterodine or tositumomab or tramadol or trametinib or trastuzumab or trastuzumab emtansine or tretinoin or trimethoprim or trimipramine) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 12879 |
| 34 | ((valproic acid or vandetanib or vardenafil or velaglucerase alfa or vemurafenib or venlafaxine or vitamin c or voriconazole or vortioxetine) and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 3988 |
| 35 | (warfarin and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 1919 |
| 36 | (zonisamide and (personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic))  | 67 |
| 37 | ((personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic) and (medicine or health or drug))  | 534951 |
| 38 |  or/15-37 limit (yr="09/09/2016 – 09/03/2016")  | 32982 |
| 39 | 14 and 38 limit (yr="09/09/2016 – 09/03/2016")  | 746 |
|  |  |  |
| **January 2016Web of Science**  |  |
| 1 | (health NEAR/2 inequalit\*) | 24161 |
| 2 | (health near/2 equit\*) | 9261 |
| 3 | (health near/2 inequit\*)  | 5374 |
| 4 | ("social gradient"\* near/3 (reduc\* or difference\* or disparit\* or increase\* or inequit\* or inequalit\* or equit\* or disadvantage\*))  | 65 |
| 5 | (“gender-based” or “gender-related” or “gender differences” or “gender factors”) | 175936 |
| 6 | ((sex or gender) near/1 (inequity or disparity or inequality))  | 15402 |
| 7 | ((ethnic$ or race or racial or religio$ or cultur$ or minorit$ or refugee or indigenous or aboriginal) near/3 (analysis or difference$ or specific or disparit$ or inequalit$ or inequit$))  | 232013 |
| 8 | (geriatrics OR homosexuality OR "disabled person")  | 429561 |
| 9 | ((poverty or low-income or socioeconomic$ or social) near/2 (analysis or disadvantage$ or specific or difference? or factor? or inequalit$ or depriv$ or inequit$ or disparit$))  | 372535 |
| 10 | ("educational status" OR socioeconomics)  | 60882 |
| 11 | ((discriminat$ or "social exclu$" or "social inclu$") near/3 (religion or culture or race or racial or aboriginal or indigenous or ethnic$))  | 164 |
| 12 | ((urban or rural or "inner-city" or slum) near/2 (difference$ or specific or analysis or inequit$ or disparit$ or inequalit$))  | 31356 |
| 13 | (("resource-poor" or ("low-income" near/1 countr$) or ("middle income" near/1 countr$) or africa or "developing countr$" or "south america" or china or asia or "latin america") near/2 (relevance or analysis or specific or difference or applicab$ or inequit$ or disparit$ or inequalit$))  | 35709 |
| 14 | (#13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1)  | 1569969 |
| 15 | (personalized medicine)  | 44905 |
| 16 | ((Abacavir or abiraterone or acetaminophen or afatinib or afutuzumab or aliskiren or amitriptyline or anastrozole or arformoterol or aripiprazole or “arsenic trioxide” or atazanavir or atomoxetine or atorvastatin or axitinib or azathioprine) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 720 |
| 17 |  ((Belimumab or boceprevir or bosutinib or "brentuximab vedotin" or busulfan) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 86 |
| 18 | ((Cabazitaxel or capecitabine or carbamazepine or "carglumic acid" or carisoprodol or carvedilol or celecoxib or ceritinib or cetuximab or cevimeline or chloroquine or chlorpropamide or cisplatin or citalopram or clobazam or clomifene or clomipramine or clopidogrel or clozapine or codeine or crizotinib) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 1977 |
| 19 | ((Dabrafenib or dapsone or darifenacin or darunavir or dasatinib or "denileukin diftitox" or desflurane or desipramine or desloratadine or dexlansoprazole or dextromethorphan or diazepam or "divalproex sodium" or doxepin or dronedarone or drospirenone) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 192 |
| 20 | ((Efavirenz or eliglustat or eltrombopag or emtricitabine or erlotinib or erythromycin or esomeprazole or ethinyl or estradiol or everolimus or exemestane) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 1299 |
| 21 | ((Fampridine or fesoterodine or fluorouracil or fluoxetine or flurbiprofen or fluvoxamine or fosamprenavir or fulvestrant) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 853 |
| 22 | ((Galantamine or gefitinib or glibenclamide or glimepiride or glipizide) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic))  | 853 |
| 23 | ((Homoharringtonine or hydralazine) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 31 |
| 24 | ((ibritumomab or ibrutinib or iloperidone or imatinib or imipramine or indacaterol or indinavir or irinotecan or isoflurane or isoniazid or “isosorbide dinitrate” or ivabradine or ivacaftor) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 836 |
| 25 | ((lansoprazole or lapatinib or lenalidomide or letrozole or lomitapide) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 106 |
| 26 | ((mafenide or maraviroc or mercaptopurine or “methylene blue” or metoclopramide or metoprolol or mipomersen or modafinil or “mycophenolic acid”) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 604 |
| 27 | ((“nalidixic acid” or nefazodone or nelfinavir or nilotinib or nitrofurantoin or norelgestromin or norfloxacin or nortriptyline) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 223 |
| 28 | ((ofatumumab or olanzapine or omeprazole) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 287 |
| 29 | ((panitumumab or pantoprazole or paroxetine or pazopanib or “peginterferon alfa-2b” or pegloticase or perphenazine or pertuzumab or “phenylacetic acid” or phenytoin or pimozide or ponatinib or posaconazole or prasugrel or pravastatin or primaquine or probenecid or propafenone or propranolol or protriptyline or pyrazinamide) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 703 |
| 30 | ((quinidine or quinine) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 134 |
| 31 | ((rabeprazole or ranolazine or rasburicase or regorafenib or rifampin or risperidone or ritonavir or rituximab or rosuvastatin or ruxolitinib) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 1046 |
| 32 | ((Sevoflurane or sildenafil or simeprevir or sirolimus or “sodium benzoate” or “sodium nitrite” or “sodium phenylbutyrate” or sofosbuvir or succimer or succinylcholine or sulfadiazine or sulfamethoxazole or sulfasalazine or sulfisoxazole or sunitinib) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 810 |
| 33 | ((tamoxifen or telaprevir or telithromycin or tenofovir or terbinafine or tetrabenazine or thioguanine or thioridazine or ticagrelor or timolol or tiotropium or tipranavir or tolterodine or tositumomab or tramadol or trametinib or trastuzumab or “trastuzumab emtansine” or tretinoin or trimethoprim or trimipramine) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 5745 |
| 34 | ((valproic acid or vandetanib or vardenafil or “velaglucerase alfa” or vemurafenib or venlafaxine or “vitamin c” or voriconazole or vortioxetine) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 740 |
| 35 | (warfarin near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)) | 1446 |
| 36 | (zonisamide near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*))  | 3 |
| 37 | ((personalised or personalized or individualised or individualized or stratified or precision or genetic or genomic or pharmacogenetic or pharmacogenomic) near/5 (medicine or health or drug))  | 190144 |
| 38 | or/15-37  | 216471 |
| 39 | 14 and 38 (yr="1999 - 2016")  | 2101 |
|  |  |  |
| **January 2016Cochrane CENTRAL and Cochrane Methods**  |  |
| 1 | (social gradient\* near/3 (reduc\* or difference\* or disparit\* or increase\* or inequit\* or inequalit\* or equit\* or disadvantage\*)):ti,ab  | 3 |
| 2 | (health near/2 (inequalit\* or equit\* or inequit\*)):ti,ab  | 135 |
| 3 | (gender-based or gender-related or gender differences or gender factors):ti,ab  | 6119 |
| 4 | ((sex or gender) near/2 (analysis or specific or difference? or factor? or inequit$ or disparit$ or inequalit$)):ti,ab  | 2731 |
| 5 | ((ethnic$ or race or racial or religio$ or cultur$ or minorit$ or refugee or indigenous or aboriginal) adj3 (analysis or difference$ or specific or disparit$ or inequalit$ or inequit$)):ti,ab  | 0 |
| 6 | MeSH descriptor: [Geriatrics] explode all trees  | 215 |
| 7 | MeSH descriptor: [Homosexuality] explode all trees | 375 |
| 8 | MeSH descriptor: [Disabled Persons] explode all trees | 1013 |
| 9 | ((poverty or low-income or socioeconomic$ or social) near/2 (analysis or disadvantage$ or specific or difference? or factor? or inequalit$ or depriv$ or inequit$ or disparit$)):ti,ab  | 582 |
| 10 | MeSH descriptor: [Educational Status] explode all trees (1264) | 1264 |
| 11 | MeSH descriptor: [Socioeconomic Factors] explode all trees (7840)  | 7840 |
| 12 | ((discriminat$ or social exclu$ or social inclu$) near/3 (religion or culture or race or racial or aboriginal or indigenous or ethnic$)):ti,ab  | 0 |
| 13 | (urban or rural or inner-city or slum) near/2 (difference$ or specific or analysis or inequit$ or disparit$ or inequalit$):ti,ab  | 12 |
| 14 | (resource-poor or (low-income adj countr$) or (middle income adj countr$) or africa or developing countr$ or south america or china or asia or latin america) near/2 (relevance or analysis or specific or difference or applicab$ or inequit$ or disparit$ or inequalit$):ti,ab  | 0 |
| 15 | MeSH descriptor: [Precision Medicine] explode all trees  | 0 |
| 16 | ((Abacavir or abiraterone or acetaminophen or afatinib or afutuzumab or aliskiren or amitriptyline or anastrozole or arformoterol or aripiprazole or arsenic trioxide or atazanavir or atomoxetine or atorvastatin or axitinib or azathioprine) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab  | 34 |
| 17 | ((Belimumab or boceprevir or bosutinib or brentuximab vedotin or busulfan) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab  | 4 |
| 18 | ((Cabazitaxel or capecitabine or carbamazepine or carglumic acid or carisoprodol or carvedilol or celecoxib or ceritinib or cetuximab or cevimeline or chloroquine or chlorpropamide or cisplatin or citalopram or clobazam or clomifene or clomipramine or clopidogrel or clozapine or codeine or crizotinib) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab  | 90 |
| 19 | ((Dabrafenib or dapsone or darifenacin or darunavir or dasatinib or denileukin diftitox or desflurane or desipramine or desloratadine or dexlansoprazole or dextromethorphan or diazepam or divalproex sodium or doxepin or dronedarone or drospirenone) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab  | 9 |
| 20 | ((Efavirenz or eliglustat or eltrombopag or emtricitabine or erlotinib or erythromycin or esomeprazole or ethinyl or estradiol or everolimus or exemestane) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab  | 40 |
| 21 | ((Fampridine or fesoterodine or fluorouracil or fluoxetine or flurbiprofen or fluvoxamine or fosamprenavir or fulvestrant) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab  | 19 |
| 22 | ((Galantamine or gefitinib or glibenclamide or glimepiride or glipizide) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab  | 2 |
| 23 | ((Homoharringtonine or hydralazine) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab  | 0 |
| 24 | ((ibritumomab or ibrutinib or iloperidone or imatinib or imipramine or indacaterol or indinavir or irinotecan or isoflurane or isoniazid or isosorbide dinitrate or ivabradine or ivacaftor) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab  | 29 |
| 25 | ((lansoprazole or lapatinib or lenalidomide or letrozole or lomitapide) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab  | 10 |
| 26 | ((mafenide or maraviroc or mercaptopurine or methylene blue or metoclopramide or metoprolol or mipomersen or modafinil or mycophenolic acid) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab (8) | 8 |
| 27 | ((nalidixic acid or nefazodone or nelfinavir or nilotinib or nitrofurantoin or norelgestromin or norfloxacin or nortriptyline) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab  | 5 |
| 28 | ((ofatumumab or olanzapine or omeprazole) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab (10) | 10 |
| 29 | (panitumumab or pantoprazole or paroxetine or pazopanib or peginterferon alfa-2b or pegloticase or perphenazine or pertuzumab or phenylacetic acid or phenytoin or pimozide or ponatinib or posaconazole or prasugrel or pravastatin or primaquine or probenecid or propafenone or propranolol or protriptyline or pyrazinamide) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab (35) | 35 |
| 30 | ((quinidine or quinine) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab  | 4 |
| 31 | ((rabeprazole or ranolazine or rasburicase or regorafenib or rifampin or risperidone or ritonavir or rituximab or rosuvastatin or ruxolitinib) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab (23) | 23 |
| 32 | ((Sevoflurane or sildenafil or simeprevir or sirolimus or sodium benzoate or sodium nitrite or sodium phenylbutyrate or sofosbuvir or succimer or succinylcholine or sulfadiazine or sulfamethoxazole or sulfasalazine or sulfisoxazole or sunitinib) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab (11) | 11 |
| 33 | ((tamoxifen or telaprevir or telithromycin or tenofovir or terbinafine or tetrabenazine or thioguanine or thioridazine or ticagrelor or timolol or tiotropium or tipranavir or tolterodine or tositumomab or tramadol or trametinib or trastuzumab or trastuzumab emtansine or tretinoin or trimethoprim or trimipramine) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab  | 39 |
| 34 | ((valproic acid or vandetanib or vardenafil or velaglucerase alfa or vemurafenib or venlafaxine or vitamin c or voriconazole or vortioxetine) near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab (9) | 9 |
| 35 | (warfarin near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab  | 53 |
| 36 | (zonisamide near/5 (personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*)):ti,ab | 0 |
| 37 | ((personalised or personalized or individualised or individualized or stratified or precision or genetic\* or genomic\* or pharmacogenetic\* or pharmacogenomic\*) near/5 (medicin\* or health\* or drug\*)):ti,ab  | 1114 |
| 38 | #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14  | 17070 |
| 39 | {or #15-#37}  | 1647 |
| 40 | #38 and #39  | 50 |

Supplementary Table S3 Inclusion criteria

|  |  |  |
| --- | --- | --- |
| Domain | Inclusion criteria | Exclusion criteria |
| Study design | Randomized controlled studies, non-randomized controlled studies, observational studies and other study types reported from 2006 onwards.  | Letters, case reports, editorials and reports of studies presented only as abstracts prior to 2010. |
| Participant population | Adults (≥16 years)  | Children (<16 years) |
| Interventions | Interventions that use biomarkers (mainly molecular) for the purpose of risk assessment, diagnosis, prognosis, monitoring and guiding therapeutic decisions. These interventions may be described as precision, individualized, stratified, personalized, genetic and/or genomic medicine.  | Interventions which do not stratify patient treatment using biomarkers or other genetic information.  |
| Outcomes | Impact of PM on health disparities. | Studies that focused on genotyping to guide efficacy and did not discuss health equity issues.  |
| Setting | The review will include evidence from studies across all settings.  | N/A |

Supplementary Table S4 GRADE quality assessment criteria

|  |  |  |  |
| --- | --- | --- | --- |
| Study Design | Quality of Evidence | Lower if | Higher if |
| Randomized trial → | High | Risk of bias-1 Serious-2 Very seriousInconsistency-1 Serious-2 Very seriousIndirectness-1 Serious-2 Very seriousImprecision-1 Serious-2 Very seriousPublication bias-1 Likely-2 Very Likely | Large effect+1 Large+2 Very largeDose response+1 Evidence of a gradientAll plausible confounding +1 Would reduce a demonstrated effect or+1 Would suggest a spurious effect when results show no effect |
|  | Moderate  |
| Observational study → | Low |
|  | Very low |