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Longitudinal exposure of English primary care patients to pharmacogenomic drugs: an analysis to inform design of pre-emptive pharmacogenomic testing

Short running title: Pharmacogenomic drugs in primary care

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Data Availability statement:

This study is based on data from CPRD obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data is provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this report are those of the authors alone. The protocol number (18_023_RA) was approved by the Independent Scientific Advisory Committee evaluation of joint protocols of research involving CPRD data in August 2018.

Word count: 3982

Atorvastatin-

<https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=2949>

Carbamazepine-

<https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=5339>

Cisplatin- <https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=5343>

Clopidogrel-

<https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=7150>

Codeine-

<https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=1673>

Daunorubicin-

<https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=7063>

Doxorubicin-

<https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=7069>

Esomeprazole-

<https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=5488>

Metoprolol-

<https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=553>

Simvastatin-

<https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=2955>

Tacrolimus-

<https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=6784>

Warfarin-

<https://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=6853>

Structured abstract

Aims. To investigate the longitudinal exposure of English primary care patients to pharmacogenomic drugs to inform design of pre-emptive testing.

Methods. Sixty-three drugs were identified with dosing guidelines based on variants of 19 pharmacogenes in the Pharmacogenomics Knowledgebase (PharmGKB) on 01/09/2018. Prescribing of these pharmacogenomic drugs between 1993-2017 was summarised for a sample of 648,141 English patients aged 50-99 on 01/01/2013, registered with Clinical Practice Research Datalink practices during 2011-12. Exposure of patients to pharmacogenomic drugs retrospectively (2, 10, 20 years) and prospectively (5 years) was described.

Results. During 2011-12, 58% of patients were prescribed at least one pharmacogenomic drug, increasing to 80% over the previous 20 years. Multiple exposure was common, with 47% patients prescribed ≥ 2 pharmacogenomic drugs and 7% prescribed ≥ 5 pharmacogenomic drugs over the next 5 years. The likelihood of exposure to pharmacogenomic drugs increased with age, with 89% patients ≥ 70 years prescribed at least one pharmacogenomic drug over the previous 20 years. Even among those aged 50-59 years, 71% were prescribed at least one pharmacogenomic drug over the previous 20 years. The pharmacogenomic drugs prescribed to the most patients were for pain relief, gastroprotection, psychiatric and cardiovascular conditions. Three pharmacogenes (*CYP2D6*, *CYP2C19* and *SLCO1B1*) accounted for $>95\%$ pharmacogenomic drugs prescribed.

Conclusions. In primary care patients, exposure to pharmacogenomic drugs is extremely common, multiplicitous and has commenced by relatively early adulthood. A small number

of pharmacogenes account for the majority of drugs prescribed. These findings could inform design of pre-emptive pharmacogenomic testing for implementation in primary care.

What is already known about this subject?

- Pharmacogenomic information can improve prescribing, but testing is currently limited in the NHS to specialist indications in small numbers of patients
- Pre-emptive multi-gene pharmacogenomic testing could inform multiple prescribing decisions over a patient's lifetime
- The optimal design of pharmacogenomic testing for use in primary care is not known

What this study adds:

- Within English primary care, multiple exposure to pharmacogenomic drugs is extremely common with 60% patients being prescribed ≥ 2 and 18% ≥ 5 pharmacogenomic drugs over 20 years
- Exposure to pharmacogenomic drugs has commenced by relatively early adulthood and increases with age
- Three pharmacogenes account for $>95\%$ pharmacogenomic drugs prescribed
- These findings could inform design of pre-emptive pharmacogenomic testing for primary care

Introduction

Pharmacogenomics is the study of how genes affect an individual's response to drugs and pharmacogenomic testing aims to provide information to improve the safety and effectiveness of drug treatment [1]. Pharmacogenomic information can be considered 'actionable' if it leads to changes in prescribing decisions, such as use of an alternative drug or dose. Medical centres in the United States now routinely offer genetic testing for common variants in genes associated with severe adverse drug reactions or poor treatment response [1-4]. However, in the United Kingdom pharmacogenomic testing is only available in a few specialist areas and has not yet been widely adopted in the National Health Service (NHS). Currently, British guidelines only mandate pre-treatment pharmacogenomic testing for abacavir and carbamazepine and then only in certain patient subgroups [5-7].

The NHS England policy document *Improving Outcomes through Personalised Medicine* [8] and the 2016 annual report of the Chief Medical Officer (England) [9] both highlight pharmacogenomics as an important opportunity to deliver precision medicine.

Implementation of pharmacogenomics is one of the three main goals of the NHS genomic revolution, along with improving outcomes from cancer and rare diseases. The NHS Genomic Medicine Service is currently determining whether pharmacogenomic testing should be included in the 2019/20 National Genomic Test Directory [10]. Pharmacogenomic testing is likely to take the form of a multi-gene panel, which can offer better value than multiple single tests as costs and processing times fall.

Pharmacogenomic testing can be pre-emptive before prescription, or reactive in response to treatment failure or an adverse drug reaction. Advantages of pre-emptive testing include availability of information at the time of prescription, allowing this to be personalised to the

patient. The use of a pre-emptive multi-gene panel has the potential to provide a lifetime's worth of test results applicable to multiple drugs. In the UK, routine contact with primary care patients, such as NHS vascular risk checks, provide opportunities for pre-emptive pharmacogenomic testing [11]. The longitudinal electronic NHS primary care record, which follows patient journeys over many years, provides an excellent vehicle for aligning pharmacogenomic information with prescribing episodes. Clinical decision support within these electronic health records could be a key tool for the integration of pharmacogenomics into routine patient care [12].

The Clinical Practice Research Datalink (CPRD) is a large database of anonymised longitudinal medical records from primary care in the UK [13]. The aim of this study was to use CPRD data to investigate the longitudinal exposure of English primary care patients to drugs where choice or dosing was affected by knowledge of pharmacogenomics (pharmacogenomic drugs). Age and frequency of exposure to pharmacogenomic drugs and the most frequent drugs and pharmacogenes involved were determined to inform design of pre-emptive multigene pharmacogenomic testing in primary care patients.

Methods

Overview

Current and historical prescribing of pharmacogenomic drugs with dosing guidelines identified in the Pharmacogenomics Knowledgebase (PharmGKB) was summarised for a sample of primary care patients in England aged 50-99 years, actively registered throughout 2011-12 in 215 practices. Exposure of patients to pharmacogenomic drugs both retrospectively (over 2, 10 and 20 years) and prospectively (5 years) was described in subgroups divided by age.

Approval

This study is based on data from CPRD obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this report are those of the authors alone. The protocol number (18_023_RA) was approved by the Independent Scientific Advisory Committee evaluation of joint protocols of research involving CPRD data in August 2018.

Population

The CPRD is a large, anonymised database of longitudinal medical records from primary care, which has been collecting data from participating UK general practices since 1987. It includes around 7% of the UK population and has been shown to be broadly representative with an age-sex structure similar to the whole population [13]. However, since CPRD is based on practices using Vision software, historically this has resulted in a geographical bias within England, with practices concentrated in the South and relatively few in the in the

North-East and East of England [14]. For this study, we selected 215 English practices, which had consented to external linkage to other datasets (about 75% of English practices) and were recording data deemed to be of research quality using internal CPRD metrics by 01/01/2012 and continued to collect such data continuously to at least 01/01/2015 [13]. All patients aged 50-99 (n=648,141) who were actively registered with these practices on 01/01/2013 and had been registered with the same practice for at least the previous 2 years were included. This provided the opportunity to analyse prescribing information back to age 30 for many individuals. For all patients, we extracted all available primary care prescribing data between 1993 and 2017, and classified exposure to pharmacogenomics drugs by searching on drug substance/generic name. Since prescribing data in CPRD is only available when the patient is registered, we could only fully describe exposure for all 684,141 patients during 2011-12. For longer retrospective periods (10, 20 years) we had to restrict to (i) practices which were contributing to CPRD at that time, (ii) patients within these practices that were registered over the whole period. Similarly, our prospective description of prescribing to 2017 is only based on patients who were still active and alive in practices still contributing to CPRD. All prescribing data over the 20 year retrospective and 5 year prospective period were extracted. **Figure 1** gives an overview of the number of practices and patients with available prescribing periods.

Selection of pharmacogenomic drugs

Drugs included in the analysis were those with well-established pharmacogenomic-based drug/ dosing guidelines in the Pharmacogenomics Knowledgebase (PharmGKB) [15].

PharmGKB provides a repository of genotype-based dosing recommendations published by the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Royal Dutch

Pharmacogenetics Working Group (DPWG), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) and/or other professional societies. Sixty-three drugs were identified as having dosing guidelines based on variants of 19 genes as of 01/09/2018 (**Table 1**).

Analysis

Exposure of patients to pharmacogenomic drugs over retrospective (over 2, 10 and 20 years) and prospective (5 years) available prescribing periods was determined and compared in subgroups divided by age on 01/01/2013. Use of a pharmacogenomic drug within an available prescribing period was defined as any prescription for a pharmacogenomic drug within that period, even where only a single prescription was recorded for a patient. Unless otherwise stated, any prescription for a pharmacogenomic drug within an available prescribing period was considered 'exposure', irrespective of whether that drug had already been prescribed to the patient prior to that time period. The pharmacogenomic drugs prescribed to the most patients and the genes most commonly implicated were identified. As exposure to pharmacogenomic drugs was not normally distributed, data were described using median (interquartile range).

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

Results

Among the 648,141 patients who were registered throughout 2011-12, complete prescribing data were further available retrospectively over 10 years (2003-12) for 538,602 patients (79%) and 20 years (1993-2012) for 289,186 patients (45%). Prescribing data were available prospectively for 203,395 patients over 5 years (2013-17) (**Figure 1**).

Prevalence of exposure to pharmacogenomic drugs

Table 2 shows the exposure of patients to pharmacogenomic drugs over available prescribing periods. Even over a two year period, 58% of patients were exposed to at least one pharmacogenomic drug (median per patient=1, IQR=0-2), and this rose to 80% among 289,185 patients with available data over the preceding 20 years (median=2, IQR=1-4). Over a five year prospective period, 47% of patients were prescribed at least two pharmacogenomic drugs and 7% were prescribed at least five pharmacogenomic drugs. When all prescriptions were counted during the study, the proportion that were for pharmacogenomic drugs rose from 16% from 1993-2012 to 20% during 2013-2017.

Supplementary figure 1 shows the distribution of the number of pharmacogenomic drugs in the different prescribing periods.

Prevalence of exposure to pharmacogenomic drugs by age

Figure 2a shows the percentage of patients prescribed pharmacogenomic drugs over available periods divided by age group. In patients aged 50-59 in 2013, 71% were exposed to at least one pharmacogenomic drug over the retrospective 20 year prescribing period and 12% were prescribed at least five pharmacogenomic drugs over the prospective 5 year period. Among patients aged 70 years and older, approximately 89% were prescribed at

least one pharmacogenomic drug, and 25% were prescribed at least five over the preceding 20 years.

Figure 2b shows incident prescribing of pharmacogenomic drugs between 2013-17 for 90,836 patients (45% of 203,395 patients with data for this period) who were not prescribed a pharmacogenomic drug during 2011-12. In this group, approximately 39% of patients aged 50-59 in 2013 were prescribed a new pharmacogenomic drug during 2013-17 after not receiving one during 2011-12. This increased across age groups to 55% of patients in the 80-89 year group. It should be noted that patients aged 90-99 are likely to be dying at a faster rate than the other age groups and therefore may not have had the chance of being prescribed a pharmacogenomic drug, hence low rates in this group.

Figure 3 shows the proportion of women and men, by age group, prescribed pharmacogenomic drugs in each year over 20 years. There was a similar increase in men and women in the prescription of pharmacogenomic drugs in all age groups over the previous 20 years. The only exception was women in the 50-59 year age group who had higher rates of pharmacogenomic drug prescribing in the mid-1990s (when they were age 30-39 years) compared to the other age categories. On review, this was due to the prescription of hormonal contraceptives for systemic use which decreases in older ages. **Figure 4** shows the cumulative exposure to pharmacogenomic drugs a 20 year period, excluding those prescribed a pharmacogenomic drug in 1993 and therefore starting from an assumption of zero pharmacogenomic drugs in those included at the start of 1993. By 2003-4 around half of patients aged 70 and over had been exposed to a pharmacogenomic drug, for patients aged 50-59 this threshold was reached during 2008.

Pharmacogenomic drugs with most frequent use

Table 3 shows the exposure of patients to individual pharmacogenomic drugs and their associated pharmacogenes. The pharmacogenomic drugs prescribed to the most patients were moderate strength opioids, proton pump inhibitors, statins, anti-depressants, hormonal contraceptives, anti-platelets and anticoagulants. Information on drugs that were only prescribed in secondary care e.g. cisplatin, daunorubicin and doxorubicin, was not available in the primary care dataset.

Pharmacogenes

The most relevant pharmacogenes for use in a primary care testing panel are *CYP2C19*, *CYP2D6*, *SLCO1B1*, *CYP2C9*, *HLA-B*, *VKORC1* and *CYP4F2* (**Table 4**). Over 20 years (1993-2012), 57% and 56% of patients had prescriptions for drugs that had dosing guidelines based on *CYP2D6* and *CYP2C19* genotypes respectively. Seven pharmacogenes (*IFNL3*, *UGT1A1*, *CFTR*, *G6PD*, *RARG*, *SLC28A3*, *UGT1A6*) were virtually never associated with a prescription in primary care. **Figure 5** indicates the cumulative impact of testing the five pharmacogenes associated with the most prescriptions; the first three pharmacogenes (*CYP2C19*, *CYP2D6* and *SLCO1B1*) account for virtually all pharmacogenomic drug prescribing (>95%) across all periods.

Discussion

Main study findings

Our results demonstrate that exposure of primary care patients to pharmacogenomic drugs is extremely common. Eight-in-ten patients were exposed to at least one pharmacogenomic drug over a 20 year period, with pharmacogenomic drugs comprising 16% of all drugs prescribed during that time. Exposure is commonly multiple, with six-in-ten patients being prescribed two or more and almost two-in-ten patients being prescribed five or more different pharmacogenomic drugs over the preceding 20 years. Prospectively, five-in-ten patients were prescribed at least two pharmacogenomic drugs over 5 years. In patients who had not been prescribed a pharmacogenomic drug in 2011-12, four-in-ten patients were prescribed at least one pharmacogenomic drug over the next 5 years.

Over two thirds of patients aged 50-59 years were prescribed at least one pharmacogenomic drug, with an average of two pharmacogenomic drugs over the previous 20 years. This indicates that a pre-emptive multi-gene panel done even at a relatively young age could have multiple applications, with the likelihood of exposure to pharmacogenomic drugs increasing with age across all available prescribing periods. Our data also highlight the pharmacogenomic drugs prescribed to the most patients in primary care and indicate that three pharmacogenes (*CYP2C19*, *CYP2D6* and *SLCO1B1*) accounted for virtually all (>95%) of these common pharmacogenomic drugs across all periods.

Comparison with other studies

Our finding that primary care patients are commonly exposed to pharmacogenomic drugs is supported by recent studies from the United States. Schildcrout and colleagues investigated

prescribing of 56 pharmacogenomic drugs in 53,000 primary care patients at Vanderbilt University Medical Centre, with a median age of 54 years at the start of the study [16]. Over a 5 year period, 65% of individuals were exposed to at least one pharmacogenomic drug and 12% were exposed to ≥ 4 . Our analysis showed similar results in a larger number of patients and over a longer period of time, whilst also providing relevance to the United Kingdom.

Samwald and colleagues investigated the prescribing of 61 pharmacogenomic drugs in 73,000,000 patients in the United States over a 4 year period (2009-12) [17]. They also compared exposure by age group. Even in the youngest age group of 0-13 years old, there was some exposure to pharmacogenomic drugs with 14% receiving at least one and 2% receiving at least two pharmacogenomic drugs. Similar to our study, they showed that exposure to pharmacogenomic drugs increased with age.

In the United States, in 2013, the 30 most commonly prescribed pharmacogenomic high-risk drugs accounted for 738 million outpatient prescriptions [18]. Samwald and colleagues showed that the most commonly prescribed pharmacogenomic drugs in their study were indicated for pain relief and cardiovascular conditions, similar to our findings [17].

Additionally, the top six pharmacogenomic drugs (simvastatin, metoprolol, esomeprazole, warfarin, atorvastatin, clopidogrel) in Schildcrout's study also featured high in our list [16].

We found that three pharmacogenes (*CYP2C19*, *CYP2D6* and *SLCO1B1*) accounted for virtually all (>95%) of these common pharmacogenomic drugs across all periods. As primary care patients are rarely exposed to more specialist pharmacogenomic drugs, this could inform design of focussed pharmacogenomic testing for implementation in primary care.

The most relevant pharmacogenes associated with the pharmacogenomic drugs in our study were *CYP2C19*, *CYP2D6*, *SLCO1B1*, *CYP2C9*, *HLA-B*, *VKORC1* and *CYP4F2*. Although we did

not have genomic data, previous studies have shown that actionable variants in these genes are extremely common. In the United States, more than 97% of the population have at least one high-risk diplotype from 12 pharmacogenes tested [18]. The PREDICT programme at Vanderbilt University Medical Centre, reported that of 10,000 patients, 91% of individuals had at least one actionable genotype among five drug-gene interactions tested (*CYP2C9/VKORC1*- warfarin, *CYP2C19*- clopidogrel, *SLCO1B1*- simvastatin, *CYP3A5*-tacrolimus and *TPMT*-thiopurines) [19]. Among 5,400 Australian patients, 96% carried at least one actionable pharmacogenomic variant in *CYP2D6*, *CYP2C1*, *CYP2C9* and *VKORC1* [20]. The Mayo clinic found that 99% of patients ($n=1,013$) had an actionable pharmacogenomic variant in *CYP2D6*, *CYP2C1*, *CYP2C9*, *VKORC1* and *SLCO1B1* [21]. Bush and colleagues reported that of 5,000 patients in the eMERGE-PGx programme, 96% of all samples had ≥ 1 actionable pharmacogenomic variant within 92 pharmacogenes [22]. The high prevalence of actionable pharmacogenomic variants is clearly of clinical importance given how common the prescribing of associated pharmacogenomic medications are in primary care patients.

Study strengths and limitations

To our knowledge, this is the first study to define the exposure of patients to pharmacogenomic drugs in a large UK primary care population over an extended period of time. Currently, there is no nationwide pre-emptive pharmacogenomic testing programme in any healthcare system. Our findings will help to define the multi-gene panel needed for pre-emptive testing in primary care patients.

While the age-sex structure of CPRD patients are broadly similar to that of the UK population [13], since CPRD is based on practices using Vision software, this has resulted in a geographical bias within England, with practices concentrated in the South and relatively

few in the in the North-East and East of England [14]. Patients registered in practices located in the North or the Midlands had marginally higher rates of being prescribed a pharmacogenomic drug (82%) over the 20-year period (1993-2012) than those patients in the South (78%). This difference was also seen in the 5-year prospective period (2013-17) with higher rates in the North/Midlands (74%) than the South (70%). These small differences would suggest that the true national prescribing prevalence of pharmacogenomic drugs might be marginally underestimated, but does not affect our overall conclusions.

A strength of our study was that we used pharmacogenomic drugs with evidence-based dosing guidelines in the PharmGKB. This indicates that pharmacogenomic testing in primary care patients could have real impact on prescribing decisions commonly made in clinical practice. The dosage of drugs used for different indications may affect the clinical significance of the drug-gene interaction e.g. codeine used as low dose for the treatment of cough vs higher doses for analgesia. However in our data set, 99% of the 5 million prescriptions for codeine were in capsule or tablet form for use as an analgesic, indicating that pharmacogenomic guidelines would apply for the majority of prescribing decisions.

The aim of our study was to inform design of pre-emptive multigene pharmacogenomic testing in primary care patients. As such our analysis only included drugs initiated in or continued in primary care and did not include drugs for specialist indications, such as chemotherapeutic, antiretroviral and antiviral medications. Our results indicate that a relatively limited pharmacogenomic testing panel would cover the majority of prescribing decisions made in primary care (**Figure 5**). Whilst a broader panel may be required to cover

specialist prescribing in secondary care, focussed reporting for primary care may assist in implementing guidelines into practice.

Within our study we were able to include patients with up to 20 years of prescribing data retrospectively and 5 years of prescribing data prospectively. This provided insight into longitudinal prescribing to individuals and their multiple exposure to pharmacogenomic drugs over time. The main weakness of our approach is that by only including patients still registered at the beginning of 2013, we are only including 'survivors' as by definition we did not include patients who have passed away prior to 2013. This means that the 90-99 year olds in 2013 in our sample are not truly representative of all 70-79 year olds in 1993. For our youngest age groups (50-59 in 2013) loss to mortality will be less of an issue, but we will not be including 30-39 year old patients from 1993 who subsequently de-registered from their General Practice over the next 20 years. Despite this, we still showed that the 30-39 year olds who were continually registered over this period were commonly exposed to pharmacogenomic drugs. Information on younger age groups is needed to identify the first opportunity for pharmacogenomic testing that would capture lifetime exposure. We also attempted to look prospectively at prescribing over the following 5 years, but only included the 'survivors' who have remained registered to practices that have continued to contribute to the CPRD over this period of time.

In our study we assessed whether patients had had any exposure to pharmacogenomic drugs in defined available prescribing periods. This allowed us to identify pharmacogenomic drugs prescribed to the most patients, enabling us to infer where pharmacogenomic testing would have potential utility in primary care. However, pharmacogenomic exposure could be defined by only a single prescription for a drug and we did not evaluate duration of

exposure or repeat exposures (e.g. to analgesic drugs). These factors would be important when considering the potential clinical utility of pharmacogenomic testing. We also defined 'exposure' as being any prescription for a pharmacogenomic drug within an available prescribing period, irrespective of whether that drug had already been prescribed to the patient prior to that time period. This approach optimised numbers of patients available for analysis and generalisability to the whole population, however it did not assess incident prescribing. In a smaller subgroup of patients not taking pharmacogenomic medicines in 2011-12 we were able to show that patients of all ages frequently received new prescriptions for pharmacogenomic drugs (**Figure 2b**).

It would have been interesting to have had the genetic profiles of the patients. The lack of genomic information limited our ability to calculate the exact number of prescribing decisions that could have been influenced for each individual. However, previous studies have shown that most people have variants in pharmacogenes that affect metabolism of common drugs and therefore our analysis is likely to have broad relevance [18-22]. The retrospective nature of the study is also a potential limitation as prescribing practice and exposure to drugs has clearly changed over the last 20 years. However, in England the 100 most commonly prescribed drugs have been remarkably consistent over the last decade and the core list of most commonly prescribed drug groups has remained stable [23].

As demonstrated in our study, a pre-emptive multi-gene panel could impact on multiple prescribing decisions throughout a patient's life. However, one recognised barrier to the implementation of pharmacogenomics into healthcare services is the lack of evidence of clinical utility. Considering this, a number of initiatives are currently being carried out to assess the clinical value of pharmacogenomic testing. For example, the Ubiquitous

Pharmacogenomics (U-PGx) consortium is leading the PREPARE trial. This is a prospective, European randomised controlled trial that will implement pre-emptive genotyping of a panel of 13 pharmacogenes consisting of 50 variants into routine care to guide drug and dose selection for 41 commonly prescribed drugs [24]. The goal of the study is to show that pre-emptive testing of patients for an entire panel of pharmacogenomic markers reduces the number of adverse drug reactions.

Implications for future research and practice

This study supports the development of a pre-emptive multi-gene panel, appropriate to primary care patients that could influence multiple prescribing decisions over the course of a patient's lifetime. Our findings could inform health economic modelling to establish the most cost-effective time at which testing should be carried out in primary care patients. There are well established points within current NHS care, for example NHS health checks offered every 5 years to all 40-74 year olds, at which this pharmacogenomic test could be introduced [11].

In conclusion, exposure of primary care patients to pharmacogenomic drugs is extremely common, multiplicitous and has commenced by relatively early adulthood. A small number of pharmacogenes account for the majority of drugs prescribed. These findings could inform design of a pre-emptive pharmacogenomic testing panel and programme for implementation in primary care.

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Author contribution statement

Emma Baker had the original idea for the study and all authors contributed to the study design. Iain Carey led the data analysis and all authors contributed to the interpretation of the data. James Kimpton wrote the first draft of the manuscript. All authors contributed to the revision of the manuscript related to its intellectual content. All authors approved the final version submitted for publication.

Conflicts of interest

The authors have no conflicts of interest to declare

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Tables

Table 1. Drugs with pharmacogenomic-based dosing guidelines from PharmGKB listed by associated gene.

Gene	Drug with pharmacogenomic-based dosing guideline
<i>CTFR</i>	ivacaftor ^a
<i>CYP2C19</i>	amitriptyline ^a , citalopram ^{a,b} , clomipramine ^a , clopidogrel ^{a,b} , doxepin ^a , escitalopram ^{a,b} , esomeprazole ^b , imipramine ^{a,b} , lansoprazole ^b , omeprazole ^b , pantoprazole ^b , sertraline ^{a,b} , trimipramine ^a , voriconazole ^{a,b}
<i>CYP2C9</i>	acenocoumarol ^b , gliclazide ^b , glimepiride ^b , phenprocoumon ^b , phenytoin ^{a,b} , warfarin ^{a,c}
<i>CYP2D6</i>	amitriptyline ^{a,b} , aripiprazole ^b , atomoxetine ^b , clomipramine ^{a,b} , codeine ^{a,b,c} , desipramine ^a , doxepin ^{a,b} , flecanide ^b , fluvoxamine ^a , haloperidol ^b , imipramine ^{a,b} , metoprolol ^b , mirtazapine ^b , nortriptyline ^{a,b} , ondasteron ^a , oxycodone ^b , paroxetine ^{a,b} , propafenone ^a , risperidone ^b , tamoxifen ^{a,b,c} , tramadol ^b , trimipramine ^a , tropisetron ^a , venlafaxine ^b , zuclopenthixol ^b
<i>CYP3A5</i>	tacrolimus ^{a,b}
<i>CYP4F2</i>	warfarin ^a
<i>DPYD</i>	capecitabine ^{a,b} , fluorouracil ^{a,b} , tegafur ^b
<i>F5</i>	hormonal contraceptives ^b
<i>G6PD</i>	rasburicase ^a
<i>HLA-A</i>	carbamazepine ^{a,b}
<i>HLA-B</i>	abacavir ^{a,b} , allopurinol ^{a,d} , carbamazepine ^{a,b} , oxcarbazepine ^a , phenytoin ^a , ribavirin ^b
<i>IFNL3</i>	peginterferon alfa-2a ^a , peginterferon alfa-2b ^a , ribavirin ^a
<i>RARG</i>	daunorubicin ^c , doxorubicin ^c
<i>SLCO1B1</i>	simvastatin ^a
<i>SLC28A3</i>	daunorubicin ^c , doxorubicin ^c
<i>TPMT</i>	azathioprine ^{a,b} , cisplatin ^c , mercaptopurine ^{a,b} , tioguanine ^{a,b}
<i>UGT1A1</i>	atazanavir ^a , irinotecan ^{a,d}
<i>UGT1A6</i>	daunorubicin ^c , doxorubicin ^c

<i>VKORC1</i>	acenocoumarol ^b , phenprocoumon ^b , warfarin ^{a,c}
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Footnote: a: CPIC guideline, b: DPWG guideline, c: CPNDS guideline, d: other guideline

CTFR= Cystic fibrosis transmembrane conductance regulator, *CYP2C19*= Cytochrome P450

2C19, *CYP2C9*=Cytochrome P450 2C9, *CYP2D6*= Cytochrome P450 2D6, *CYP3A5*=

Cytochrome P450 3A5, *CYP4F2*= Cytochrome P450 4F2, *DPYD*= Dihydropyrimidine

dehydrogenase, *F5*= Coagulation factor V, *G6PD*= Glucose-6-phosphate dehydrogenase,

HLA-A= Human leukocyte antigen-A, *HLA-B*= Human leukocyte antigen-B, *IFNL3*= Interferon

lambda 3, *RARG*= Retinoic acid receptor gamma, *SLCO1B1*= Solute carrier organic anion

transporter family member 1B1, *SLC28A3*= Solute carrier family 28 member 3, *TPMT*=

Thiopurine S-methyltransferase, *UGT1A1*= UDP-glucuronosyltransferase family 1 member

A1, *UGT1A6*= UDP-glucuronosyltransferase family 1 member A6, *VKORC1*= Vitamin K

epoxide reductase complex subunit 1 (Key: *Gene*=Protein)

The following drugs with pharmacogenomic-based dosing guidelines are not licensed for prescription in the UK: phenprocoumon, tropisetron, and desipramine.

Table 2. Exposure of patients to pharmacogenomic (PGx) drugs over available prescribing periods

Available prescribing periods	Before 1/1/2013			After 1/1/2013
	2 years (2011-2012)	10 years (2003-2012)	20 years (1993-2012)	5 years (2013-2017)
Total practices with complete recording throughout period	215	215	159	82
Total patients registered throughout period	684,141	538,602	289,186	203,395
- With ≥ 1 prescription for any drug, n(%)	596,767 (87%)	517,843 (96%)	283,948 (98%)	190,035 (93%)
- With ≥ 1 prescription for any PGx drug, n(%)	399,311 (58%)	400,422 (74%)	231,113 (80%)	143,947 (71%)
PGx drugs				
- Mean per patient	1.2	2.1	2.5	1.7
- Median (IQR)	1 (0-2)	2 (0-3)	2 (1-4)	1 (0-3)
Number of patients with multiple PGx Drugs				
- With ≥ 2 PGx drugs, n(%)	222,796 (33%)	284,238 (53%)	172,818 (60%)	95,454 (47%)
- With ≥ 5 PGx drugs, n(%)	17,879 (3%)	67,465 (13%)	50,769 (18%)	14,448 (7%)

Table 3. Exposure to individual pharmacogenomic (PGx) drugs licensed for prescription in the UK over available prescribing periods

PGx drug	Available prescribing period								Corresponding pharmacogene(s)
	-2 Years (2011-2012) N=684,141		-10 Years (2003-2012) N=538,602		-20 Years (1993-2012) N=289,186		+5 Years (2013-2017) N=203,395		
	n	%	n	%	n	%	n	%	
codeine	136997	20%	221623	41%	139784	47%	66463	33%	<i>CYP2D6</i>
omeprazole	140142	20%	170784	32%	100499	34%	70433	35%	<i>CYP2C19</i>
simvastatin	156472	23%	168050	31%	94681	32%	44472	22%	<i>SLCO1B1</i>
lansoprazole	68613	10%	103676	19%	65873	22%	29809	15%	<i>CYP2C19</i>
amitriptyline	52717	8%	84654	16%	58064	19%	27917	14%	<i>CYP2D6, CYP2C19</i>
tramadol	45784	7%	79492	15%	46585	16%	19074	9%	<i>CYP2D6</i>
citalopram	39295	6%	58446	11%	34553	12%	15061	7%	<i>CYP2C19</i>
warfarin	26479	4%	28395	5%	17951	6%	9042	4%	<i>CYP2C9, VKORC1, CYP4F2</i>
paroxetine	3850	1%	8643	2%	16405	6%	1263	0.6%	<i>CYP2D6</i>
clopidogrel	20030	3%	28392	5%	16232	5%	11607	6%	<i>CYP2C19</i>
hormonal contraceptives	883	0%	5935	1%	15909	5%	143	0.1%	<i>F5</i>
sertraline	13176	2%	17878	3%	13733	5%	9812	5%	<i>CYP2C19</i>
gliclazide	20569	3%	20184	4%	11951	4%	7601	4%	<i>CYP2C9</i>
allopurinol	15322	2%	15520	3%	9171	3%	6409	3%	<i>HLA-B</i>
mirtazapine	10760	2%	14314	3%	8120	3%	5924	3%	<i>CYP2D6</i>
carbamazepine	5214	1%	9079	2%	8090	3%	1849	1%	<i>HLA-A, HLA-B</i>
venlafaxine	5425	1%	10472	2%	7667	3%	2238	1%	<i>CYP2D6</i>
esomeprazole	5470	1%	12150	2%	7155	2%	3119	2%	<i>CYP2C19</i>
pantoprazole	3706	1%	8601	2%	6644	2%	1962	1%	<i>CYP2C19</i>
tamoxifen	2909	0.4%	6470	1%	5145	2%	1062	0.5%	<i>CYP2D6</i>
escitalopram	3022	0.4%	9390	2%	4611	2%	1066	0.5%	<i>CYP2C19</i>
fluorouracil	4197	0.6%	8129	2%	4576	2%	3764	2%	<i>DPYD</i>
nortriptyline	2767	0.4%	4778	0.9%	3859	1%	1507	0.7%	<i>CYP2D6</i>
metoprolol	3435	0.5%	5040	0.9%	3446	1%	881	0.4%	<i>CYP2D6</i>
clomipramine	867	0.1%	1618	0.3%	2680	0.9%	291	0.1%	<i>CYP2C19, CYP2D6</i>

imipramine	616	0.1%	1423	0.3%	2225	0.8%	167	0.1%	<i>CYP2C19, CYP2D6</i>
oxycodone	2786	0.4%	4012	0.7%	2108	0.7%	1700	0.8%	<i>CYP2D6</i>
azathioprine	1841	0.3%	2500	0.5%	1792	0.6%	736	0.4%	<i>TPMT</i>
phenytoin	2139	0.3%	2256	0.4%	1741	0.6%	589	0.3%	<i>CYP2C9, HLA-B</i>
trimipramine	438	0.1%	902	0.2%	1710	0.6%	116	0.1%	<i>CYP2C19, CYP2D6</i>
glimepiride	2204	0.3%	2676	0.5%	1646	0.6%	1103	0.5%	<i>CYP2C9</i>
flecainide	1742	0.3%	2196	0.4%	1511	0.5%	832	0.40%	<i>CYP2D6</i>
risperidone	1958	0.3%	2479	0.5%	1409	0.5%	665	0.3%	<i>CYP2D6</i>
haloperidol	921	0.1%	1466	0.3%	1273	0.4%	237	0.1%	<i>CYP2D6</i>
doxepin	343	0.1%	999	0.2%	1251	0.4%	101	0.1%	<i>CYP2C19, CYP2D6</i>
tacrolimus	997	0.2%	1662	0.3%	887	0.3%	713	0.4%	<i>CYP3A5</i>
ondansetron	466	0.1%	736	0.1%	475	0.2%	422	0.2%	<i>CYP2D6</i>
fluvoxamine	58	0.0%	131	0.0%	433	0.2%	27	0.0%	<i>CYP2D6</i>
aripiprazole	604	0.1%	579	0.1%	269	0.1%	315	0.2%	<i>CYP2D6</i>

Values are number (%) patients prescribed individual pharmacogenomic drugs licensed for prescription in the UK over available prescribing periods

Drugs are ranked from most to least commonly prescribed over the -20 year prescribing period. Drugs not included in the table were:

Rarely prescribed in primary care (number of prescriptions over 20 year period):

propafenone (n=186), mercaptopurine (n=92), oxcarbazepine (n=97), acenocoumarol (n=106), zuclopenthixol (n=108), voriconazole (n=9), peginterferon alfa-2a (n=2), ribavirin (n=4), tioguanine (n=1), abacavir (n=0), atazanavir (n=0), atomoxetine (n=1), capecitabine (n=0).

Not prescribed at all in primary care during any available prescribing period: cisplatin, daunorubicin, doxorubicin, irinotecan, ivacaftor, peginterferon alfa-2b, rasburicase, tegafur

Table 4. Exposure to drugs by related pharmacogenes over available prescribing periods

Available prescribing period	-2 Years (2011-2012)		-10 Years (2003-2012)		-20 Years (1993-2012)		+5 Years (2013-2017)	
	n	%	n	%	n	%	n	%
<i>CYP2D6</i>	202516	30%	275145	51%	170388	57%	87650	43%
<i>CYP2C19</i>	257079	38%	285659	53%	165780	56%	109782	54%
<i>SLCO1B1</i>	156472	23%	168050	31%	94681	32%	44472	22%
<i>CYP2C9</i>	50250	7%	51496	10%	31897	11%	17717	9%
<i>HLA-B</i>	22459	3%	26252	5%	18253	6%	8773	4%
<i>VKORC1</i>	26648	4%	28488	5%	17983	6%	9094	4%
<i>CYP4F2</i>	26479	4%	28395	5%	17951	6%	9042	4%
<i>F5</i>	883	0.1%	5935	1%	15909	5%	143	0.1%
<i>HLA-A</i>	5214	0.8%	9079	2%	8090	3%	1849	0.9%
<i>DPYD</i>	4198	0.6%	8132	2%	4576	1.5%	3764	2%
<i>TPMT</i>	1936	0.3%	2585	0.5%	1829	0.6%	795	0.4%
<i>CYP3A5</i>	997	0.2%	1662	0.3%	887	0.3%	713	0.4%
<i>IFNL3</i>	3	0.0%	5	0.0%	4	0.0%	1	0.0%
<i>UGT1A1</i>	0	0.0%	2	0.0%	0	0.0%	1	0.0%
<i>CFTR</i>	0	0.0%	0	0.0%	0	0.0%	0	0.0%
<i>G6PD</i>	0	0.0%	0	0.0%	0	0.0%	0	0.0%
<i>RARG</i>	0	0.0%	0	0.0%	0	0.0%	1	0.0%
<i>SLC28A3</i>	0	0.0%	0	0.0%	0	0.0%	0	0.0%
<i>UGT1A6</i>	0	0.0%	0	0.0%	0	0.0%	0	0.0%

Values are number (%) of patients prescribed any drug with drug/ dosing guidelines related to individual pharmacogenes over available prescribing periods. Pharmacogenes are ranked from most to least commonly associated with a prescribed drug over the -20 year prescribing period.

Figure 1

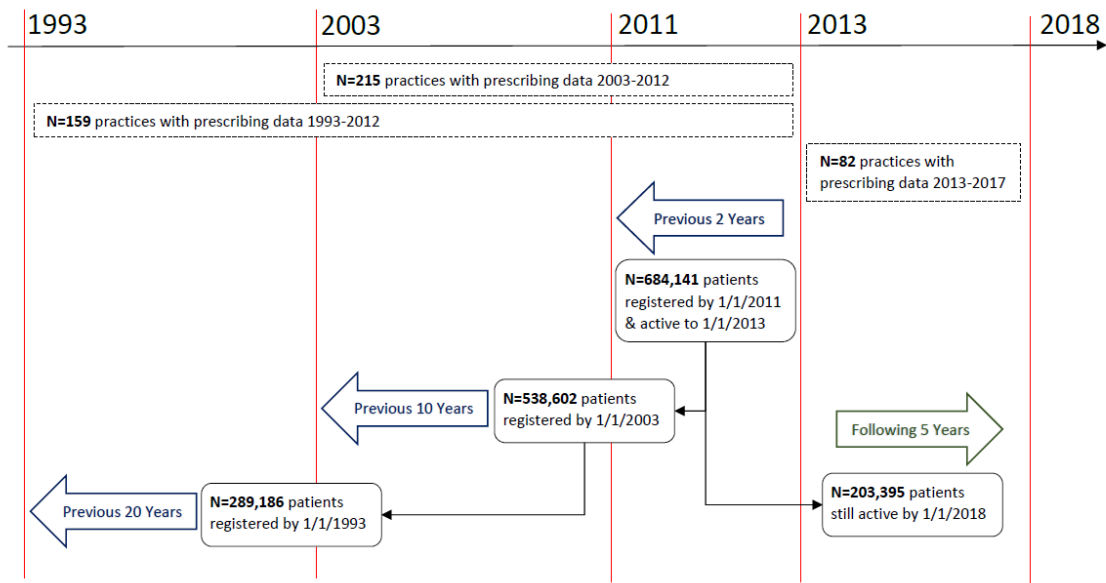


Figure 1. Overview of practices and patients included in available prescribing periods

Accepted

Figure 2a

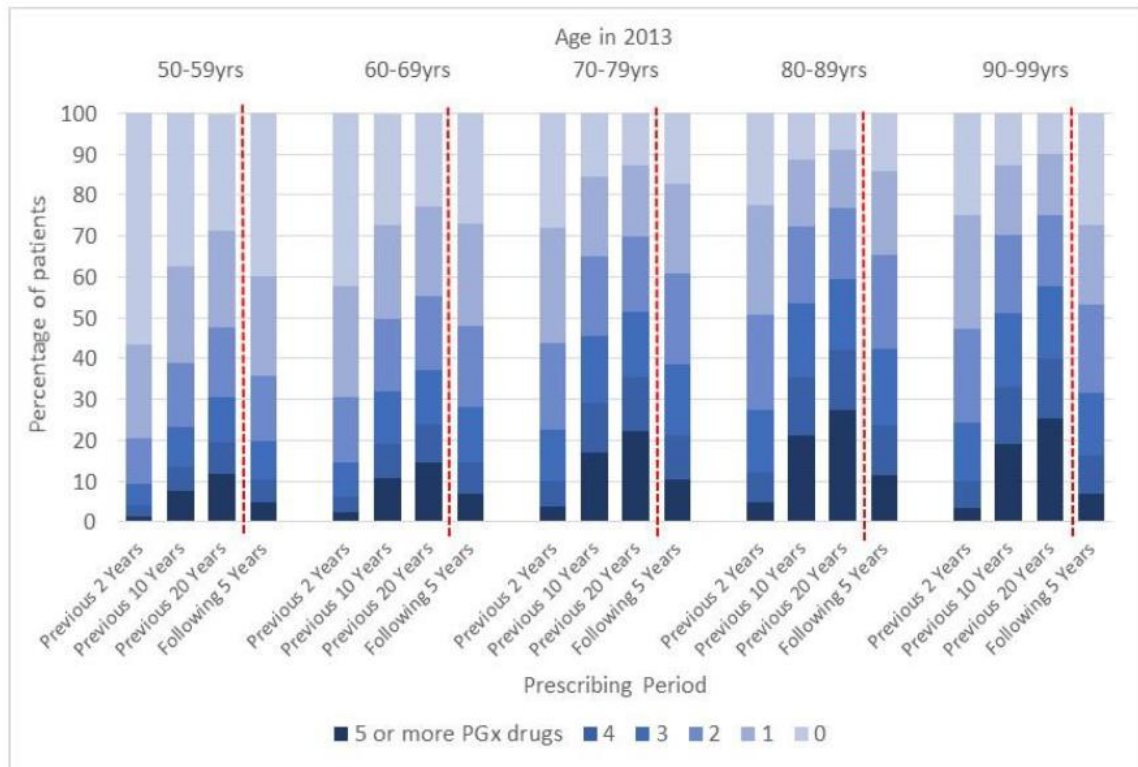


Figure 2a. Percentage of patients prescribed pharmacogenomic drugs over available prescribing periods by patient age in 2013

Accepted

Figure 2b

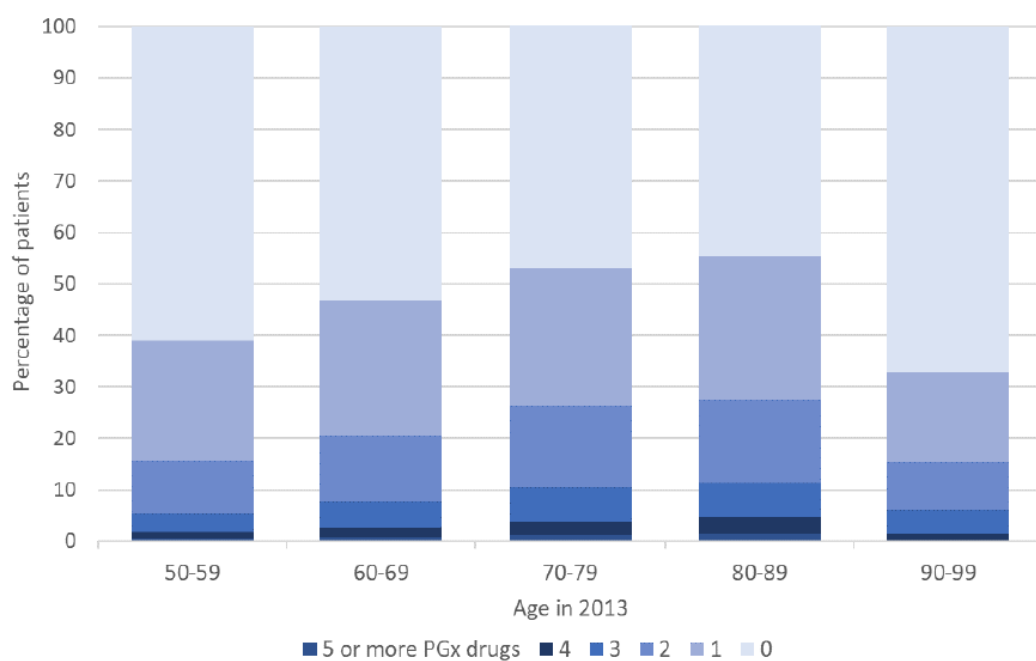


Figure 2b. Percentage of patients with a prescription for a pharmacogenomic drug in 2013-17 among those with no prescriptions for pharmacogenomic drugs during 2011-12, by patient age in 2013

Accepted

Figure 3

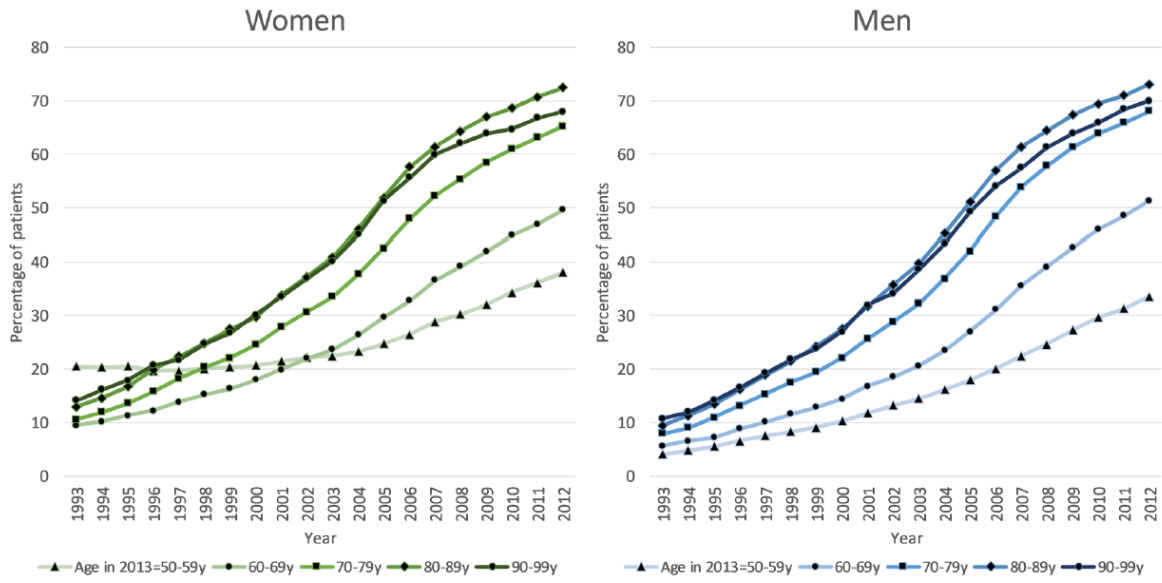


Figure 3. Annual percentage of patients prescribed at least one pharmacogenomic drug for different age groups in women and men over retrospective 20 year prescribing period (1993-2012)

Accepted

Figure 4

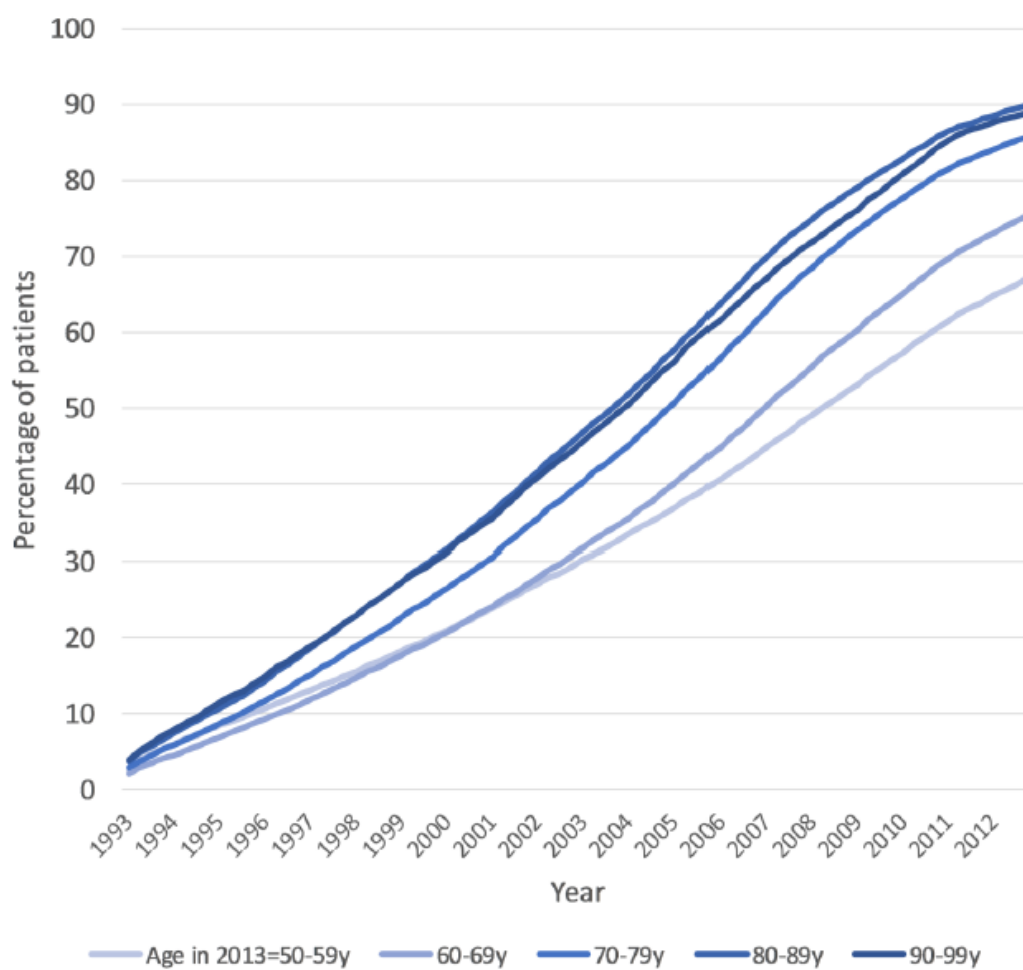


Figure 4. Cumulative percentage of patients prescribed at least one pharmacogenomic drugs over 20 years

As we did not have pre-1993 prescribing data, we excluded patients who were prescribed a pharmacogenomic drug at any time in 1993 and then looked for first exposure afterwards.

Figure 5

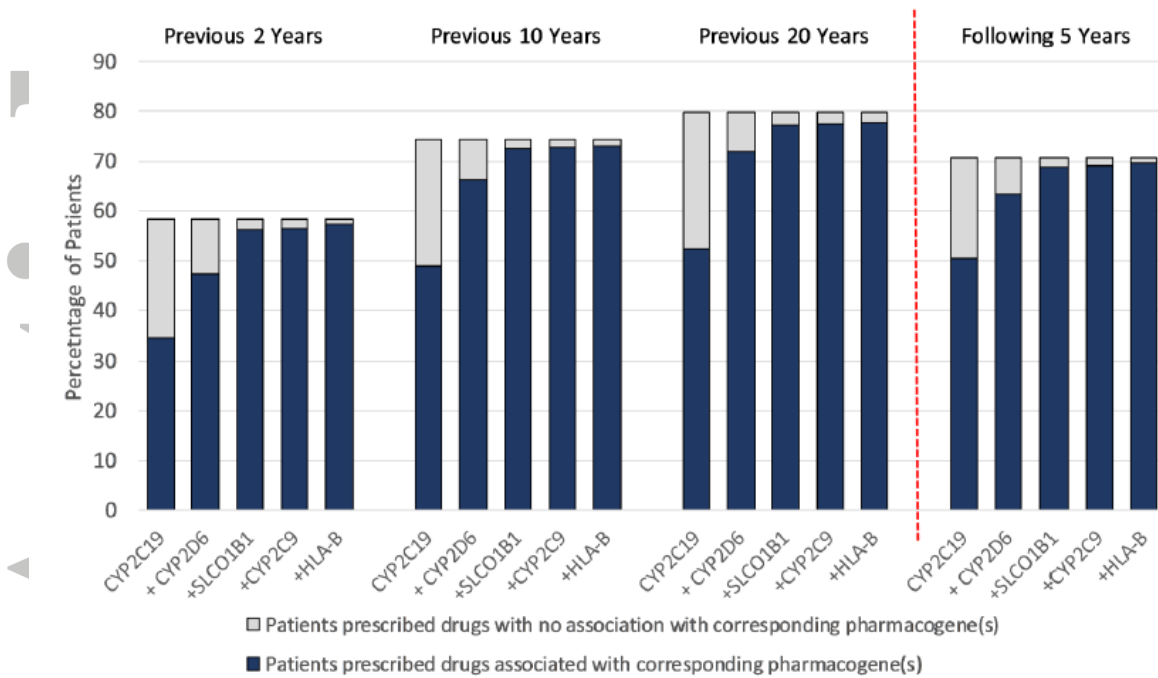


Figure 5. Cumulative impact of testing the five pharmacogenes associated with the most prescriptions over available prescribing periods

The overall height of the bars shows the percentage of patients in each prescribing period exposed to drugs affected by any pharmacogene. Blue bars show the cumulative effect of adding the five most common pharmacogenes successively from left to right. Grey bars indicate the proportion of patients prescribed drugs associated with pharmacogenes not yet considered (when moving left to right on the x-axis).

For each period, the first blue bar represents the % of patients prescribed any drug influenced by CYP2C19 only. The second blue bar is then % of patients with any drug which corresponds to CYP2C19 or CYP2D6 or both. And so on.