Value of Pharmacogenetic Testing Assessed with Real-World Drug Utilization and Genotype Data

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Implementation of pharmacogenetic testing in clinical care has been slow and with few exceptions is hindered by the lack of real-world evidence on how to best target testing. In this retrospective register-based study, we analyzed a nationwide cohort of 1,425,000 patients discharged from internal medicine or surgical wards and a cohort of 2,178 university hospital patients for purchases and prescriptions of pharmacogenetically actionable drugs. Pharmacogenetic variants were obtained from whole genome genotype data for a subset ($n = 930$) of the university hospital patients. We investigated factors associated with receiving pharmacogenetically actionable drugs and developed a literature-based cost–benefit model for pre-emptive pharmacogenetic panel testing. In a 2-year follow-up, 60.4% of the patients in the nationwide cohort purchased at least one pharmacogenetically actionable drug, most commonly ibuprofen (25.0%) and codeine (19.4%). Of the genotyped subset, 98.8% carried at least one actionable pharmacogenetic genotype and 23.3% had at least one actionable gene-drug pair. Patients suffering from musculoskeletal or cardiovascular diseases were more prone to receive pharmacogenetically actionable drugs during inpatient episode. The cost–benefit model included frequently dispensed drugs in the university hospital cohort, comprising ondansetron (19.4%), simvastatin (7.4%), clopidogrel (5.0%), warfarin (5.1%), (es)citalopram (5.3%), and azathioprine (0.5%). For untargeted pre-emptive pharmacogenetic testing of all university hospital patients, the model indicated saving €17.49 in direct healthcare system costs per patient in 2 years without accounting for the cost of the test itself. Therefore, it might be reasonable to target pre-emptive pharmacogenetic testing to patient groups most likely to receive pharmacogenetically actionable drugs.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Majority of people carry at least one actionable pharmacogenetic genotype, and the value of pharmacogenetic testing is widely accepted. However, only few studies have assessed the utility and cost-effects of pre-emptive pharmacogenetic testing in a scenario where all patients admitted to hospital would be genotyped.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We aimed to determine prevalence of known pharmacogenetic variants, incidence of pharmacogenetically actionable drugs, and frequency of actionable gene-drug pairs in a cohort of hospital-treated Finnish patients. Furthermore, we investigated which factors associate with receiving pharmacogenetically actionable drugs, and estimated cost-effects of untargeted pre-emptive pharmacogenetic panel testing with a cost–benefit model.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Actionable pharmacogenetic variants and associated drugs are overall very common in the Finnish population, although elderly patients, patients suffering from cardiovascular and musculoskeletal diseases, as well as patients undergoing procedures are more often exposed to pharmacogenetically actionable drug treatment. Untargeted pre-emptive pharmacogenetic panel testing showed modest cost-saving potential when considering direct healthcare expenditure only.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Our findings highlight the importance of clinical implementation studies on pre-emptive pharmacogenetic panel testing and suggest that it might be reasonable to utilize targeted pre-emptive pharmacogenetic testing in selected patient groups instead of an unselected testing strategy.

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Pharmacogenetic variants account for a substantial amount of individual variability in drug response,[1] and majority of people carry at least one actionable pharmacogenetic genotype.[2–6] These become clinically relevant and might require an intervention from the treating physician if an associated drug is prescribed. Unsuitable drugs can predispose patients to adverse drug reactions (ADRs), or poor efficacy resulting in therapeutic failure.[1]

Accumulating evidence and the decreasing costs of pharmacogenetic testing makes it as a potential tool to improve drug efficacy and preventing ADRs. A physician can utilize pre-emptive pharmacogenetic testing to adjust patient's pharmacotherapy proactively. In a recent review of pharmacogenetic studies on polypharmacotherapy, five out of six studies reported improved clinical outcomes, decrease in ADRs and the number of drugs used, or reduced utilization of healthcare services when pharmacogenetic testing results were integrated into clinical decision support tools.[7] In many therapeutic areas, targeted pre-emptive pharmacogenetic testing has been shown to be cost-saving or cost-neutral.[8] Furthermore, the Ubiquitous Pharmacogenomics (U-PGx) consortium recently published a randomized controlled trial showing that pharmacogenetically guided prescribing could reduce ADRs by 30% in patients with relevant drugs.[9]

Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have published evidence-based pharmacogenetic prescribing guidelines to help physicians implement pharmacogenetic test results into clinical practice. At the time of writing this article, CPIC had compiled 26 guidelines for more than 140 drugs and 23 associated genes (https://cpicpgx.org/). While the effects of genetic variation on drug response are well understood, guidelines or drug labelling rarely take a stand on whether to test pharmacogenetic variants. As such, pre-emptive pharmacogenetic testing is routinely conducted only when initiating a limited number of drugs, such as fluoropyrimidines, thiopurines, and abacavir.[10]

Several potential barriers are delaying clinical implementation of pre-emptive pharmacogenetic testing, including limited data on pharmacogenetic gene-drug pair frequencies, physicians' inexperience with pharmacogenetic testing, absence of guidelines clearly stating in which clinical situations to test patients, and lack of cost–benefit analyses on pharmacogenetic testing panels.[11] The aim of this study was to overcome some of these barriers by utilizing real-world drug dispensation and healthcare encounter data. In this retrospective register-based study, we analyzed drug consumption data of pharmacogenetically actionable drugs, and applied biobank data to determine frequencies of pharmacogenetic variants and actionable gene-drug pairs in two cohorts of the Finnish population. One cohort consists of adult patients hospitalized either to surgical or internal medicine ward. The other cohort consists of adult participants of the FINRISK Study,[12] a population survey studying risk factors of chronic, noncommunicable diseases in Finland. In addition, we analyzed predicting factors for receiving pharmacogenetically actionable drugs during inpatient episode and developed a cost–benefit model for untargeted pre-emptive pharmacogenetic testing.

METHODS

Study population

This study consists of two separate cohorts drawn from retrospective register data. We formed the first study population, hereafter referred to as the nationwide cohort, from the Care Register for Health Care in Finland, which is a mandatory register collecting care notifications from all institutions providing health care.[13] Individuals fulfilling the following criteria were included: (i) an inpatient episode in a public hospital in mainland Finland providing specialist care in either a surgical or internal medicine ward between January 1, 2008, and December 31, 2014, and (ii) at least 18 years old patients with an individual Finnish personal identity code.

For the second cohort, the HUS Helsinki University Hospital cohort, hereafter referred to as the HUS cohort, we analyzed the National FINRISK Study cohort data spanning from 1992 to 2012 that had been transferred to the THL Biobank. The FINRISK Study cohorts have been comprehensively described previously.[12] At least 18 years old patients were included in the HUS cohort if (i) they participated in the National FINRISK Study in 1992, 1997, 2002, 2007, or 2012, (ii) they had any inpatient episode exceeding 24 hours in the HUS Helsinki University Hospital between January 1, 2010, and March 31, 2016, and (iii) the information of their inpatient episodes was obtainable from electronic health records.

Study drug identification

We included a drug to the study if (i) the drug had an associated actionable CPIC prescribing guideline, (ii) the drug was available on the Finnish market, and (iii) the drug was administered via either oral or parenteral route. Additionally, in the nationwide cohort, we excluded drugs not reimbursed by the Social Insurance Institution of Finland. In the nationwide and the HUS cohort drug consumption analyses, CPIC prescribing guidelines published by the time of the data collection (October 2020 and November 2018, respectively), were utilized, including all three recommendation classification levels (strong, moderate, and optional).[14–32]

Study design and use of register data

Each patient was followed for 2 years (nationwide cohort) or eight calendar quarters (HUS cohort) starting from the initial inpatient episode. We defined the primary outcome as the first post-discharge drug purchase of any of the pharmacogenetically actionable drugs, and additionally for the HUS cohort, the first prescription of any pharmacogenetically actionable drug during any inpatient episode. We defined the

prevalent drug use as any purchase of the pharmacogenetically actionable drugs 6 months (nationwide cohort) or two quarters (HUS cohort) before the start of the initial inpatient episode. The incidence of initiation of pharmacogenetically actionable drugs during the follow-up time was calculated by excluding any prevalent drugs from the data. For the HUS cohort incidence, we also included pharmacogenetically actionable drugs initiated during any prospective inpatient episodes, including the drugs initiated during the initial inpatient episode. Drug purchase data were obtained from the nationwide prescription register administered by the Social Insurance Institution in Finland and prescription data during the inpatient episodes from the HUS electronic patient records (**Figure 1**).

Furthermore, we categorized the drugs according to their associated pharmacogenes and calculated gene-specific incidences. Prescriptions of pharmacogenetically actionable drugs, patients' diagnoses, procedures, and the specialty of the treating ward during the initial inpatient episode were obtained from electronic health records. We categorized the medical specialty of the initial inpatient episode to surgical, other operative, psychiatric, internal medicine, or another conservative ward.

Genotyping

In this study, we analyzed a total of 30 pharmacogenetic variants from 10 genes from a subset of the HUS cohort ($n = 930$, **Supplementary Methods**, **Table S10**). We chose the variants based on the abovementioned CPIC guidelines. A variant was included if there was substantial evidence linking the variant to clinical phenotype, and it was known to have a relatively high allelic frequency in the Finnish (or European) population. Furthermore, we combined genotype data with drug utilization data and defined the amount of actionable gene-drug pairs for the cohort subset. An actionable gene-drug pair was defined as an actionable pharmacogenetic genotype and a prescription for an associated drug.

Additionally, we examined a separate genotyping cohort, hereafter referred to as the PGx panel cohort, to validate results gained from the HUS cohort genotypes and to investigate the frequencies of actionable genotypes in selected additional genes that were not available in the FINRISK data (**Supplementary Methods**, **Table S11**). A total of 967 unrelated healthy Finnish volunteers from previous pharmacogenetic studies formed the PGx panel cohort.[33–35] The cohort was genotyped utilizing an accredited 12 gene pharmacogenetic panel test covering clinically relevant variants found in the Finnish or major continental populations.

Statistical analysis

Drug dispensation, inpatient episode, and genotype data together with demographic details were summarized by descriptive statistics. The 95% confidence intervals were calculated for the HUS cohort only, as the nationwide cohort covered the entire Finnish population. SAS System for Windows, version 9.4 (SAS Institute, Cary, NC, USA) was used for analyses of the nationwide cohort data. Hardy–Weinberg equilibrium (HWE) P values were calculated for all variants using JMP Genomics version 8, with Bonferroni correction for multiple testing. For the HUS cohort, a binary logistic regression model on IBM SPSS Statistics (version 25) was used to define factors that predict inpatient prescriptions of the pharmacogenetically actionable drugs during the initial inpatient episode.

Cost–benefit analysis

We created a 1-year state-transition cost–benefit model to assess possible cost-savings of untargeted pre-emptive pharmacogenetic testing (**Supplementary Methods**, **Figures S1–S8b**, **Tables S1–S8b**). A drug was included in the model if (i) it was commonly prescribed for the HUS cohort patients and (ii) a clinical outcome due to either poor efficacy or an ADR well-described in the literature is associated with the drug, (iii) the clinical outcome is associated with pharmacogenetic variation, and (iv) the clinical outcome is relatively common.

Ethical aspects

For the nationwide cohort, the current study was conducted within approvals by the National Institute for Health and Welfare of Finland (permission no: THL/2245/5.05.00/2019), the Social Insurance Institution of Finland (91/522/2015), and the Statistics Finland (TK-53-484-20).

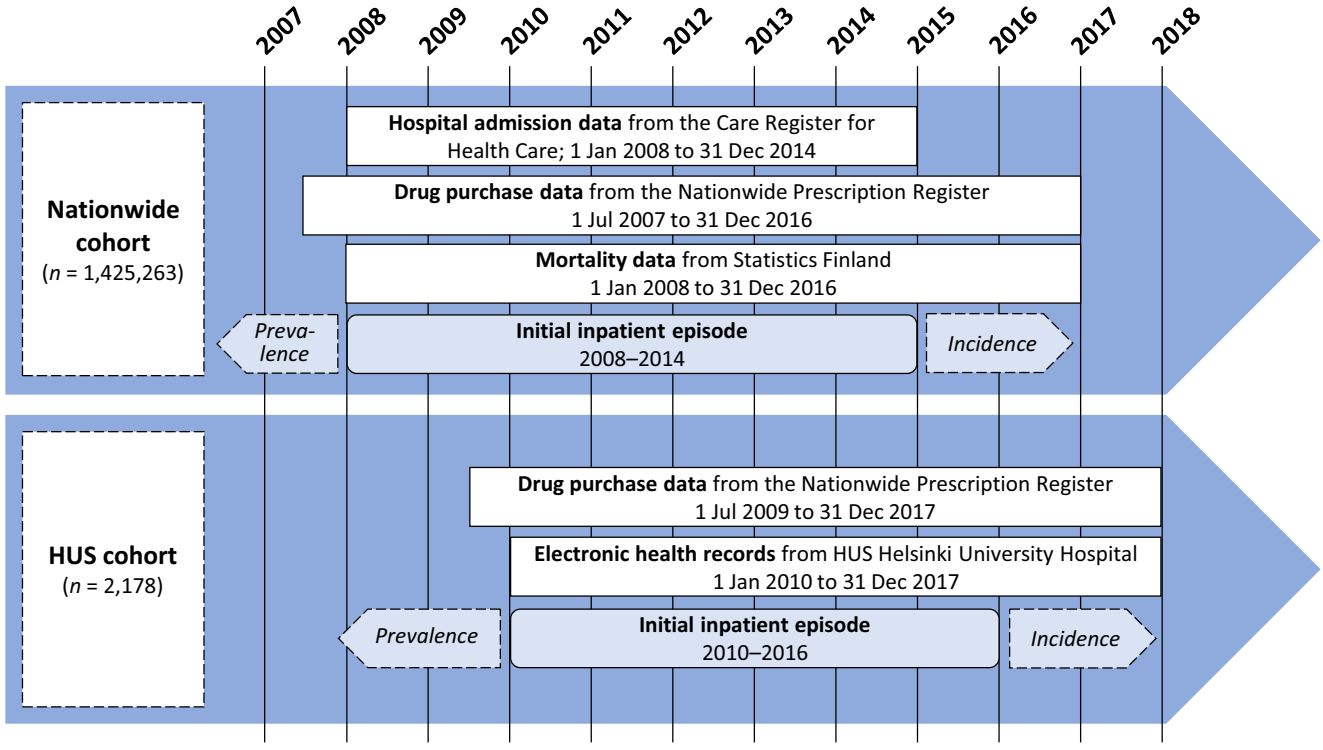

Figure 1 Overview of the study design and registers used.

As no human subjects were recruited within this cohort, no informed consent was needed. For the HUS cohort, all subjects had given their written informed consent. The information and the blood samples of the research subjects were transferred to the THL Biobank pursuant to the Finnish Biobank Law (688/2012). Within the scope of the current study, the subjects were not contacted. For the PGx cohort, the study protocols were approved by the Ethics committee of the Hospital District of Helsinki and Uusimaa (record numbers: 48/E0/07, 267/13/03/00/2011, 86/13/03/00/2015), and all participants gave a written informed consent.

RESULTS

Prevalence and incidence of pharmacogenetically actionable drugs

The proportion of women was 49.8% in the nationwide cohort and 55.4% in the HUS cohort (**Table S9**). Majority (69.8% and 54.0%) of the patients were surgical in both cohorts. Before the initial inpatient episode, simvastatin (14.6%), ibuprofen (14.1%), pantoprazole (7.1%), warfarin (6.6%), and codeine (6.6%) were the most prevalent pharmacogenetically actionable drugs in the nationwide cohort. In the HUS cohort, simvastatin (18.0%), codeine (12.5%), warfarin (8.9%), citalopram (3.0%), and escitalopram (3.0%) were the most prevalent (**Table 1**). During the initial inpatient episode, pharmacogenetically actionable drugs were prescribed to 37.6% of the HUS cohort patients (**Figure 2**). Five of the most commonly prescribed drugs during the initial inpatient episode were ondansetron (14.6%), simvastatin (12.1%), codeine (10.3%), warfarin (6.4%), and clopidogrel (3.2%) (**Table 1**). During the 2-year follow-up, patients in the nationwide cohort most often purchased ibuprofen (25.0%), codeine (19.4%), pantoprazole (12.5%), simvastatin (5.9%), and warfarin (5.4%). In the HUS cohort, incidence was highest for codeine (21.5%), ondansetron (19.4%), simvastatin (7.4%), warfarin (5.1%), and clopidogrel (5.0%) (**Table 1**; **Figure 3**). At the end of the 2-year follow-up, at least one pharmacogenetically actionable drug was dispensed for 60.4% of the nationwide cohort patients and 49.8% of the HUS cohort patients (**Figure 2**). Azathioprine, (es)citalopram, clopidogrel, ondansetron, simvastatin, and warfarin accounted for 59.1% of the drug initiations for the HUS cohort patients at the end of the follow-up. In the nationwide cohort, drug initiations were associated most frequently with *CYP2C9* (29.1%), *CYP2C19* (19.9%), and *CYP2D6* (19.9%) (**Figure 3**). In the HUS cohort, *CYP2D6* (44.5%), *CYP2C19* (13.0%), and *SLCO1B1* (7.4%) were the most frequent (**Figure 3**).

Predicting factors for inpatient prescriptions

With a binary logistic regression analysis, we identified 13 predictors associated with a prescription of pharmacogenetically actionable drug during the initial inpatient episode of HUS cohort patients. Factors that increased the likelihood of receiving pharmacogenetically actionable drugs included diseases of the circulatory and nervous system, endocrine, nutritional, and metabolic diseases, and diseases of the musculoskeletal system and connective tissue, as well as old age and undergoing any procedure during the first inpatient episode (**Table 2**).

Actionable genotypes

Pharmacogenetic variants were common both in the HUS cohort and the PGx panel cohort as 98.8% and 98.2% of the subjects, respectively, carried at least one actionable genotype (**Figure 4**; **Table S12**). On average, each HUS cohort patient carried three actionable genotypes. *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP4F2*, *SLCO1B1*, and *VKORC1* had a high proportion (over 20%) of actionable genotypes, and the genotyping results of the two cohorts were concordant with each other (**Figure 4**; **Table S10**). Furthermore, by the end of the follow-up time, 23.3% of the HUS cohort had at least one actionable gene-drug pair. Majority (18.8%) of the actionable gene-drug pairs were related to *CYP2D6*, followed by *CYP2C19* (6.5%), *VKORC1* (3.5%), *CYP2C9* (3.3%), *SLCO1B1* (3.1%), *CYP4F2* (2.6%), and *DPYD* (0.2%).

Cost–benefit analysis

We simulated the cost–benefit model with azathioprine, (es)citalopram, clopidogrel, ondansetron, simvastatin, and warfarin. These drugs accounted for 59.1% of the prescriptions for the HUS cohort patients during the 2-year follow-up. We excluded codeine as the probabilities of pharmacogenetic variability-induced clinical consequences could not be estimated based on the literature. Our cost–benefit model implemented for HUS cohort patients and their drug dispensation data indicated that at the end of the follow-up time, untargeted pre-emptive pharmacogenetic testing of all university hospital patients would save €7.49 per patient of direct healthcare costs in specialized health care, and a total of €17.49 per patient in both primary and specialized health care. For the nationwide cohort, the estimated savings were €7.14 and €16.35, respectively. Warfarin and clopidogrel showed most cost-saving potential, as they accounted for 46.7% and 42.3% of healthcare cost reduction when considering both specialized and primary health care. For other drugs, azathioprine accounted for 8.8%, simvastatin for 1.2%, (es)citalopram for 0.6%, and ondansetron for 0.2% of the potential cost-savings. Percutaneous coronary intervention as an indication accounted for 81.2%, stroke 17.7%, and acute coronary syndrome 1.1% of the cost-saving potential of clopidogrel in specialized health care. Primary health care included, the proportions were 51.5%, 47.9%, and 0.5%, respectively.

DISCUSSION

These data demonstrate that pharmacogenetically actionable drugs and pharmacogenetic variants as well as actionable gene-drug pairs are highly frequent in hospital-treated patients. According to our cost–benefit model, untargeted pre-emptive pharmacogenetic testing could lead to modest direct healthcare cost-savings in 2-year follow-up without considering the cost of the test itself. In addition, several factors associated with inpatient prescription of pharmacogenetically actionable drugs, which can potentially be used to identify patient groups most likely benefiting from pre-emptive pharmacogenetic testing.

The initiated pharmacogenetically actionable drugs were most frequently associated with *CYP2C9*, *CYP2C19*, *CYP2D6*, and *SLCO1B1*. Our findings are in concordance with previous studies,[36–38] although, the most frequently associated genes strongly depend on the drugs included in a particular study. Pharmacogenetically actionable drugs were frequently used in the Finnish population, as up to 60% of the studied patients were exposed to at least one of the pharmacogenetically actionable drugs

Table 1 Prevalence, inpatient prescriptions, and 2-year incidence of the studied pharmacogenetically actionable drugs in a cohort of Finnish surgical and internal medicine ward patients (nationwide cohort, *n* = 1,425,263) and a cohort of Finnish university hospital patients (HUS cohort, *n* = 2,178)

	Prevalence, % (95% CI)		Inpatient prescriptions, % (95% CI)	Two-year incidence, % (95% CI)	
Therapy area/drug (Associated gene or allele)	Nationwide cohort	HUS cohort	HUS cohort	Nationwide cohort	HUS cohort[a]
Antidepressants					
Amitriptyline (*CYP2C19, CYP2D6*)	1.58	0.9 (0.6–1.4)	1.5 (1.1–2.1)	1.13	2.1 (1.5–2.8)
Citalopram (*CYP2C19*)	2.95	3.0 (2.3–3.8)	1.8 (1.4–2.5)	1.88	2.7 (2.1–3.4)
Clomipramine (*CYP2C19, CYP2D6*)	<0.10	<0.1	0.0	<0.10	<0.1
Doxepin (*CYP2C19, CYP2D6*)	0.31	0.4 (0.2–0.7)	<0.1	0.17	<0.1
Escitalopram (*CYP2C19*)	2.01	3.1 (2.4–3.9)	1.6 (1.1–2.2)	2.18	2.6 (2.0–3.3)
Fluvoxamine (*CYP2D6*)	<0.10	<0.1	0.0	<0.10	0.0
Nortriptyline (*CYP2D6*)	<0.10	<0.1	0.1 (0.05–0.4)	0.11	0.3 (0.2–0.7)
Paroxetine (*CYP2D6*)	0.36	0.3 (0.2–0.7)	0.2 (0.1–0.5)	0.16	0.2 (0.1–0.5)
Sertraline (*CYP2C19*)	0.67	0.5 (0.3–0.9)	0.2 (0.1–0.5)	0.56	0.5 (0.3–0.9)
Trimipramine (*CYP2C19, CYP2D6*)	<0.10	<0.1	0.0	<0.10	<0.1
Antiemetics					
Ondansetron (*CYP2D6*)	N/A	0.2 (0.1–0.5)	14.6 (13.2–16.2)	N/A	19.4 (17.8–21.1)
Tropisetron (*CYP2D6*)	N/A	<0.1	0.0	N/A	<0.1
Antiepileptics					
Carbamazepine (*HLA-A*31:01, HLA-B*15:02*)	0.72	0.9 (0.6–1.4)	0.6 (0.4–1.1)	0.30	0.3 (0.2–0.7)
Phosphenytoin (*CYP2C9, HLA-B*15:02*)	N/A	0.0	0.0	N/A	<0.1
Oxcarbazepine (*HLA-B*15:02*)	0.40	0.3 (0.1–0.6)	0.2 (0.1–0.5)	0.24	0.5 (0.3–0.9)
Phenytoin (*CYP2C9, HLA-B*15:02*)	0.14	<0.1	<0.1	<0.10	0.1 (0.05–0.4)
Antigouts					
Allopurinol (*HLA-B*58:01*)	2.20	2.9 (2.3–3.7)	1.6 (1.1–2.2)	1.65	1.6 (1.1–2.2)
Antimycotics					
Voriconazole (*CYP2C19*)	<0.10	0.0	0.0	<0.10	<0.1
Antineoplastic agents					
Capecitabine (*DPYD*)	0.13	0.2 (0.1–0.5)	<0.1	0.65	1.2 (0.9–1.8)
Mercaptopurine (*TPMT, NUDT15*)	<0.10	0.0	0.0	<0.10	<0.1
Tamoxifen (*CYP2D6*)	N/A	0.7 (0.4–1.1)	<0.1	0.57	0.7 (0.5–1.2)
Thioguanine (*TPMT, NUDT15*)	0.0	0.0	0.0	<0.10	0.0
Antithrombotics					
Clopidogrel (*CYP2C19*)	0.87	1.4 (1.0–2.0)	3.2 (2.5–4.0)	4.12	5.0 (4.2–6.0)
Warfarin (*VKORC1, CYP2C9, CYP4F2*)	6.61	8.9 (7.8–10.2)	6.4 (5.5–7.5)	5.42	5.1 (4.3–6.2)
Cholesterol-lowering					
Simvastatin (*SLCO1B1*)	14.62	18.0 (16.5–19.7)	12.1 (10.8–13.5)	5.87	7.4 (6.4–8.6)
Detoxificants in oncolytics					
Rasburicase (*G6PD*)	N/A	0.0	0.0	N/A	<0.1
Immunosuppressants					
Azathioprine (*TPMT, NUDT15*)	0.41	0.4 (0.2–0.7)	0.3 (0.2–0.7)	0.39	0.5 (0.2–0.8)
Tacrolimus (*CYP3A5*)	<0.10	<0.1	<0.1	<0.10	<0.1
NSAIDs					
Celecoxib (*CYP2C9*)	0.65	N/A	N/A	0.92	N/A
Ibuprofen (*CYP2C9*)	14.13	N/A	N/A	25.04	N/A
Meloxicam (*CYP2C9*)	1.98	N/A	N/A	3.06	N/A

(Continued)

Table 1 (Continued)

Therapy area/drug (Associated gene or allele)	Prevalence, % (95% CI)		Inpatient prescriptions, % (95% CI)	Two-year incidence, % (95% CI)	
	Nationwide cohort	HUS cohort	HUS cohort	Nationwide cohort	HUS cohort[a]
Piroxicam (*CYP2C9*)	<0.10	N/A	N/A	0.0	N/A
Opioids					
Codeine (*CYP2D6*)	6.64	12.5 (11.2–13.9)	10.3 (9.1–11.7)	19.36	21.5 (19.8–23.3)
Proton pump inhibitors					
Lansoprazole (*CYP2C19*)	3.87	N/A	N/A	4.13	N/A
Omeprazole (*CYP2C19*)	2.30	N/A	N/A	4.15	N/A
Pantoprazole (*CYP2C19*)	7.06	N/A	N/A	12.50	N/A
Psychostimulants					
Atomoxetine (*CYP2D6*)	<0.10	N/A	N/A	<0.10	N/A

The following drugs had no purchases or prescriptions: abacavir, atazanavir, desipramine, fluorouracil, imipramine, ivacaftor, peginterferon alpha-2a, peginterferon alpha-2b, and ribavirin.CI, confidence interval; HUS, HUS Helsinki University Hospital; N/A, not assessed; NSAIDs, Nonsteroidal anti-inflammatory drugs.
[a]Includes both inpatient prescriptions and new drug purchases.

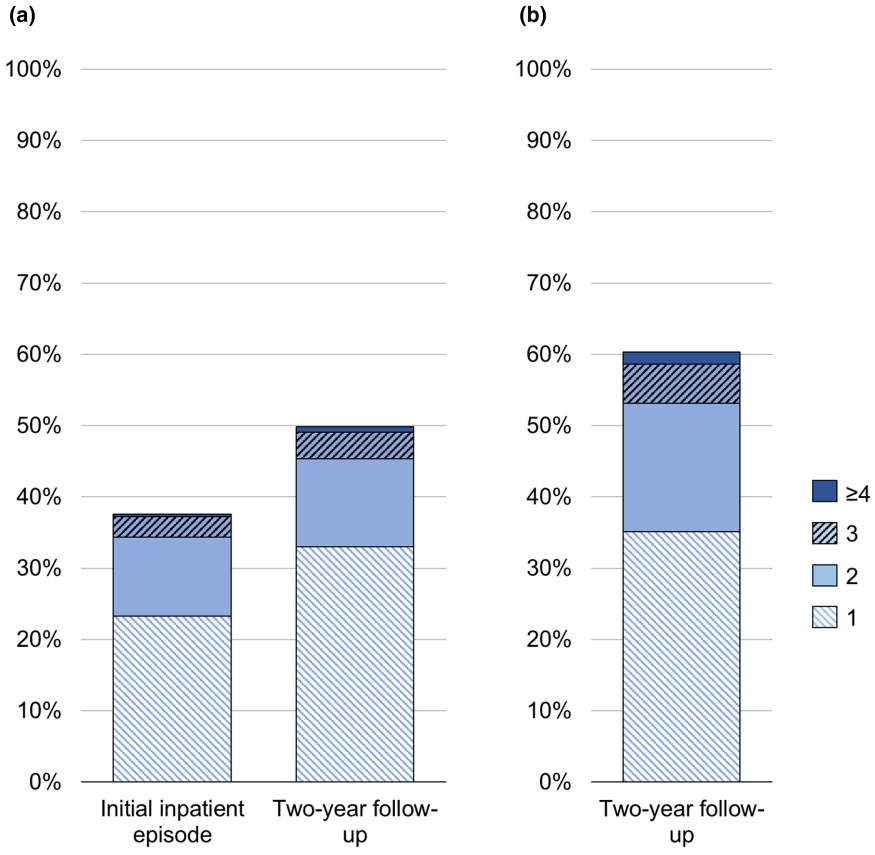

Figure 2 Number of pharmacogenetically actionable drugs per patient (a) during the initial inpatient episode and in 2-year follow-up in the HUS cohort (n=2,178), and (b) in 2-year follow-up in the nationwide cohort (n=1,425,263).

during the 2-year follow-up. Similar or even higher exposure rates have been reported in previous studies.[36,39,40] In the present study, hospitalization markedly increased the initiation of some drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), codeine, ondansetron, pantoprazole, and clopidogrel. Majority of the patients in both cohorts were surgical, whereas majority of the hospital inpatients in the United States are medical.[41] The most commonly prescribed drugs in our study seem to reflect this high number of surgical patients. In the nationwide cohort, ibuprofen was the most commonly initiated pharmacogenetically actionable

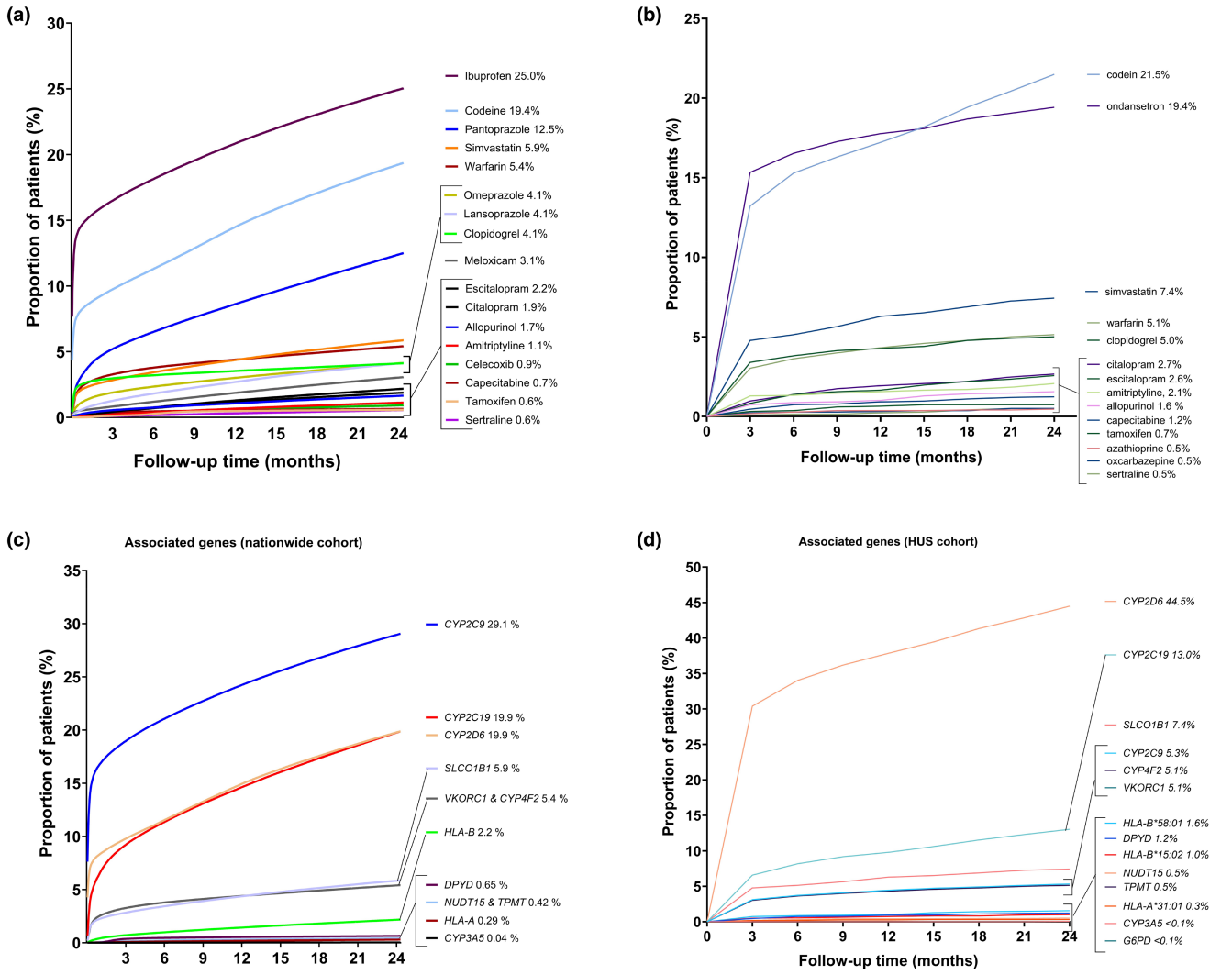

Figure 3 Pharmacogenetically actionable drug utilization incidences in 2-year follow-up. (a) Drug initiations in a nationwide cohort of 1,425,263 Finnish hospital-treated patients, and (b) in the HUS cohort of 2,178 hospital-treated patients in the HUS Helsinki University Hospital area. (c and d) The drug initiation incidences according to associated genes in the nationwide cohort and in the HUS cohort, respectively.

drug, which is consistent with its status as a first-line choice in treating postoperative pain. Since ibuprofen is also commonly sold over-the-counter in Finland, the exposure rate in our study likely underestimates its real-world consumption. However, the clinical significance of ibuprofen pharmacogenetics is relatively low, since ibuprofen is typically used as short regimens, and non-genetic factors play a major role in individual risk for ADRs.

Proton pump inhibitors (PPIs) were prescribed to one in five patients during the 2-year follow-up. PPIs are often co-administered with NSAIDs to prevent NSAID-induced gastrointestinal irritation and ulcers. The frequent initiation of ibuprofen could partly explain the high use of PPIs after the initial inpatient episode. Codeine was also very commonly initiated, which probably reflects the current pain management practices. High ondansetron exposure rate seen in the HUS cohort seems to be linked to pharmacotherapy of the surgical patients. Additionally, ondansetron is widely used in cancer patients to treat nausea and vomiting associated with chemotherapy and radiation therapy. Our findings on the most frequently used drugs were in concordance with drug incidences in previous reports.[39,42] Notably, data for the HUS cohort were gathered before CPIC published guidelines for PPIs and NSAIDs, while these guidelines were included in the nationwide cohort data, which led to differences in drug incidence rates between our cohorts. Moreover, data on ondansetron were not available from the nationwide cohort. However, the use of ondansetron in outpatient setting is relatively rare.

Cardiovascular drugs were frequently initiated and simvastatin was among the five most commonly used drugs in both cohorts. Interestingly, although simvastatin was frequently used before the initial inpatient episode, hospitalization did not seem to increase simvastatin initiations and the 2-year incidence rates in both cohorts were distinctly low. Simvastatin initiations have decreased over the years, and it is possible that existing simvastatin therapy has been switched to a more potent statin such as rosuvastatin or atorvastatin. The utility of pharmacogenetic testing to guide

Table 2 Predictors for inpatient prescription of the pharmacogenetically actionable drugs during the initial inpatient episode in the HUS cohort ($n = 2,178$)

	OR (95% CI)	*P* value
Age ≥77 years	1.4 (1.1–1,7)	3.8×10^{-3}
Treatment period under other operative specialties[a]	0.48 (0.32–0.72)	3.9×10^{-4}
Any procedure	1.6 (1.0–2.3)	0.028
Procedures (Finnish procedure classification)		
Of the endocrine system	0.38 (0.16–0.88)	7.3×10^{-3}
Of the chest wall, pleura, mediastinum, diaphragm, trachea, bronchus, and lung	0.68 (0.54–0.86)	1.3×10^{-3}
Of the gastrointestinal system	1.4 (1.1–1.8)	0.011
Of the female reproductive organs	2.0 (1.1–3.5)	0.026
Systemic procedures	1.4 (1.1–1.8)	2.5×10^{-3}
Unlocalized diagnostic procedures	1.5 (1.1–2.1)	7.9×10^{-3}
Diagnosis during the initial inpatient episode (ICD-10)		
Endocrine, nutritional, and metabolic diseases (E00-E90)	1.9 (1.4–2.7)	1.4×10^{-4}
Diseases of the nervous system (G00-G99)	1.9 (1.3–2.8)	2.4×10^{-3}
Diseases of the circulatory system (I00-I99)	1.8 (1.4–2.3)	1.4×10^{-5}
Diseases of the musculoskeletal system and connective tissue (M00-M99)	1.8 (1.4–2.4)	5.0×10^{-6}

[a]Emergency medicine, anesthesiology, intensive care, phoniatrics, otorhinolaryngology, gynecology, and obstetrics and ophthalmology. ICD-10, International Classification of Diseases 10th Revision.

lipid-lowering pharmacotherapy is increasing as the updated CPIC guideline for statins now includes dosing recommendations also for other statins.[43] Clopidogrel was another frequently initiated cardiovascular drug. Impaired activation of clopidogrel due to pharmacogenetic variants in *CYP2C19* can have detrimental outcomes for the patient.[14] Warfarin was likewise frequently used both before the hospital admission and after discharge. Although directly acting anticoagulants are increasingly favored over vitamin K antagonists, warfarin is still highly important in treating patients with an artificial heart valve and, especially in low-income countries, also for other indications.

We identified several factors associated with a prescription for a pharmacogenetically actionable drug during the inpatient episodes. One such factor was undergoing procedures during the inpatient episodes, which is mostly explained by the use of ondansetron and analgesics. Moreover, diagnosis of musculoskeletal diseases, which typically require treatment with analgesics, as well as cardiovascular diseases were also strongly associated with receiving a prescription for a pharmacogenetically actionable drug. Other associating factors included diseases of the nervous system, endocrine, and metabolic diseases and advanced age. Elderly patients in particular could benefit from pharmacogenetic testing, as they are exposed to polypharmacotherapy and are known to be susceptible to ADRs due to age-related changes in physiology.[44] Our findings may be helpful in targeting pharmacogenetic testing to patient groups where its utility is highest.

Previous studies have reported that 91–98.8% of the studied patients have at least one pharmacogenetically actionable genotype.[2–6] Our results verify that the frequencies of the studied variants in Finns are mainly in concordance with the European reference population (**Figure 4**; **Table S10**). Due to a founder effect and population bottlenecks, the Finnish population has significant enrichment of low-frequency loss-of-function and missense variants.[45] Accordingly, we found that the frequency of *NUDT15* intermediate metabolizers, a known risk factor for severe thiopurine-related hematopoietic toxicity,[46] was markedly higher in our cohort than in other European populations (4.2% vs. 0.6–0.8%).[6,24] Our results suggest that patients of Finnish origin are at higher risk for experiencing myelotoxic effect of thiopurine treatment, which can be prevented by pharmacogenetic testing. Additionally, as previously described,[47] a markedly higher proportion of ultrarapid CYP2D6 metabolizers was found in the Finnish population compared with other European populations (4.7–6.0 vs. 2.3%).[48]

By combining genotype data with individual drug utilization data, we demonstrated that almost one in four patients had at least one actionable gene-drug pair. Similar results have been reported previously in other studies.[6,39,42] *CYP2D6* accounted for the majority of the actionable gene-drug pairs; half of the patients carrying an actionable *CYP2D6* genotype had a prescription for an associated drug. In a previous study in primary care setting, *CYP2C19* constituted most of the gene-drug interactions.[39] The high proportion of *CYP2D6*-associated gene-drug interactions in our study reflects the frequent use of codeine and ondansetron.

Our study appears to be the first to assess the utility and cost-effects of pre-emptive pharmacogenetic testing in a scenario where all patients admitted to hospital are genotyped. The cost–benefit model indicates that modest cost-savings can be achieved with untargeted pre-emptive pharmacogenetic testing without accounting for the costs of the test itself. Of the six drugs included in the model, clopidogrel and warfarin had most cost-saving potential, as they both have expensive-to-treat ADRs or poor response-related outcomes, which may be prevented with pre-emptive pharmacogenetic testing.[49,50] Recent systematic review suggests that targeted pharmacogenetic testing is cost-effective for many gene-drug pairs, but limited data have existed for pre-emptive and multigene testing.[8] Majority of the studies on clopidogrel and antidepressants have indicated cost-efficacy, but studies on antiepileptics and warfarin have shown varying results.[8]

Significant regional variation can be expected in the outcomes of pharmacoeconomic studies on pharmacogenetic testing, and many factors, such as genetic ancestry, willingness-to-pay thresholds, and healthcare costs, can influence the results. Therefore, the results of our cost–benefit model cannot be directly applied to other healthcare systems due to varying expenditures. Finland has relatively low expenses in health care, with no fixed willingness-to-pay thresholds. In 2020 healthcare expenditures were €4,030.85 per capita, ranking Finland in the middle of the Organisation for Economic Co-operation and Development

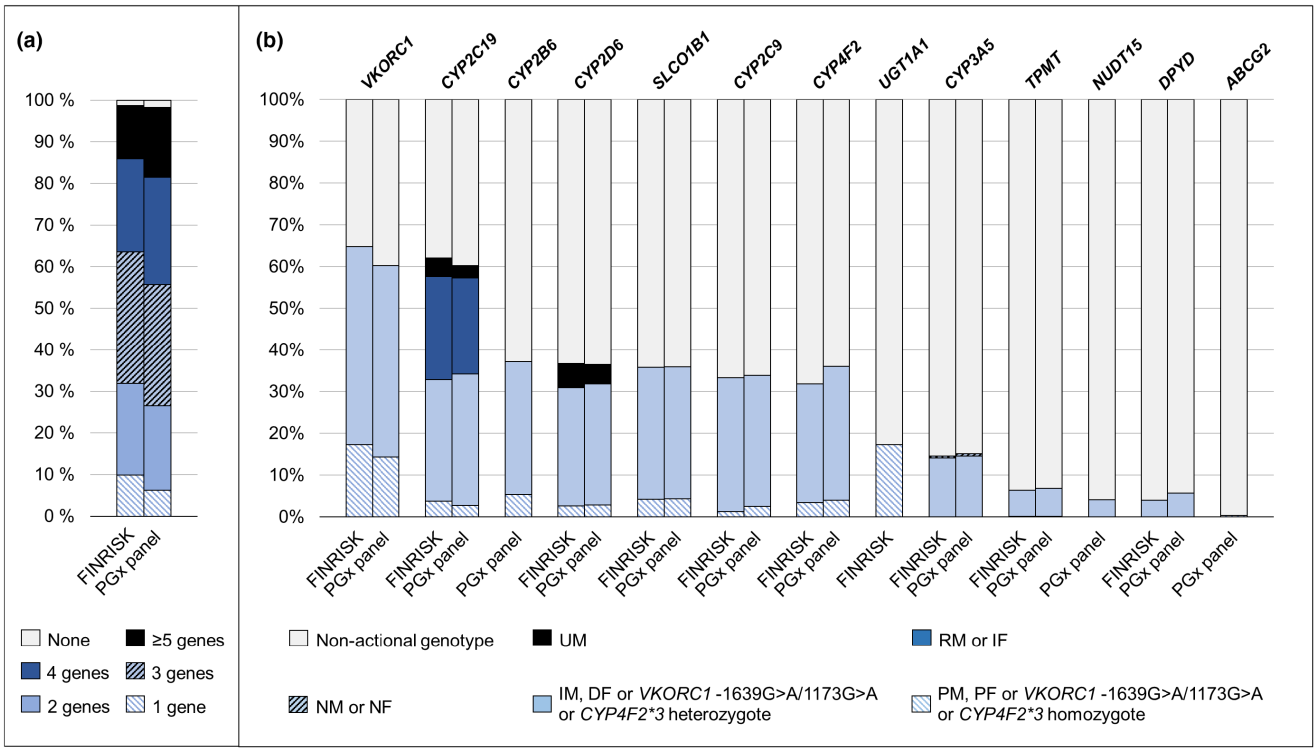

Figure 4 (a) Number of actionable genotypes per patient and (b) the distribution of pharmacogenetic actionable genotypes in the subset of the HUS cohort participants ($n=930$) and in the PGx panel cohort ($n=967$). *CYP3A5* normal metabolizer frequency is represented by the black diagonal stripes on light blue background and *ABCG2* poor function frequency (0.41%) is represented by the light blue diagonal stripes on white background. DF, decreased function; IF, increased function; IM, intermediate metabolizer; NF, normal function; NM, normal metabolizer; PF, poor function; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer.

(OECD) Member countries. However, when applying local cost- and genotype frequency parameters and drug utilization data, our cost–benefit model can be utilized to estimate the direct healthcare cost-effects associated with pre-emptive pharmacogenetic testing. Despite its limitations, our cost–benefit model represents a conservative estimate of the possible cost-savings associated with pre-emptive pharmacogenetic testing. We concentrated solely on direct healthcare costs, and excluded all outpatient medication, pension, and insurance costs. They could represent substantial expenses in the total cost-effects of pharmacogenetic testing. We chose to model six common pharmacogenetically actionable drugs accounting for almost 60% of all of the prescriptions, but many frequently used drugs were not included in the model. Furthermore, we simulated a scenario where every patient admitted to a hospital would be tested. By targeting the pharmacogenetic testing to patients most likely to benefit from the testing could result in higher cost-savings.

We chose the CPIC guidelines as the reference for pharmacogenetically actionable drugs. Slight differences, however, exist between different guidelines and drug labels. The DPWG has published genotype-based dosing recommendations on aripiprazole and risperidone, whereas the CPIC has a recommendation on NSAIDs. In general, drug labels rarely contain pharmacogenetic dosing recommendations.[10] Adoption of all evidence-based pharmacogenetic recommendations would likely result in greater benefits than seen in the present study.

Our study has several strengths. We were able to form an inclusive sample of population in our study comprising over 1.4 million adult patients, which represents ~26% of the total Finnish population. We used comprehensive national registers with complete follow-up on drug purchases. By combining data from different registers with genetic data obtained from a biobank, detailed individual-level information could be obtained. However, the study also has some limitations. The drug utilization data in our two study cohorts was not completely compatible, as the HUS cohort's data collection was done before CPIC had published guidelines for PPIs and NSAIDs, and ondansetron purchase data were not available in the nationwide cohort. In addition, we were unable to include pharmacogenetically actionable *HLA* risk alleles in our genotype data. Furthermore, our cohorts had a high proportion of surgical patients and therefore the results cannot be directly extrapolated to hospital settings with higher proportion of internal medicine patients. Additionally, in the cost–benefit model, the follow-up time was limited to 2 years, and with longer timeframe the cost-savings would likely be higher. Despite its limitations, pre-emptive pharmacogenetic testing can provide additional information to ensure safe and efficient drug therapy in combination with other clinical factors, such as age, renal function, liver function, and polypharmacotherapy.

Based on our results, targeting pre-emptive pharmacogenetic testing for patients suffering from cardiovascular diseases, patients undergoing procedures requiring the use of analgesics and antiemetics,

as well as for elderly patients may be beneficial. Pharmacogenetically actionable cancer medications and genetic variants associated with them were not particularly common in our study. However, utilizing pre-emptive pharmacogenetic testing when pharmacogenetic variation can predispose patients to fatal drug toxicity (e.g., fluoropyrimidines and thiopurines) should be strongly considered. Since 2020, the European Medicines Agency has recommended screening of patients for dihydropyrimidine dehydrogenase enzyme deficiency before treatment with fluoropyrimidines.

To conclude, our data indicate that a significant number of hospital-treated patients could potentially benefit from pharmacogenetics-guided prescribing, as both the pharmacogenetically actionable drugs and actionable genotypes were highly common. Although our cost–benefit model resulted in only moderate cost-savings from untargeted pre-emptive pharmacogenetic testing, targeting the patients most likely to receive pharmacogenetically actionable drugs might have greater cost-saving potential.

SUPPORTING INFORMATION

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

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CONFLICT OF INTEREST

All authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

Kaisa Litonius, Noora Kulla, Aleksi Tornio, and Mikko Niemi wrote the manuscript, designed and performed the research, and analyzed the data. Petra Falkenbach, Kati Kristiansson, Arto Orpana, Tommi Nyrönen, and Markus Perola designed and performed the research. Katriina Tarkiainen and Ville Kytö designed and performed the research and analyzed the data. Liisa Ukkola-Vuoti, Mari Korhonen, Sofia Khan, Johanna Sistonen, and Mats Lindstedt performed the research. Kristiina Cajanus and Miia Turpeinen designed the research.

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