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Original article

The effect of pharmacogenetic profiling with a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy

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Abstract

Objective:

To compare healthcare resource utilization (HRU) and clinical decision-making for elderly patients based on cytochrome P450 (CYP) pharmacogenetic testing and the use of a comprehensive medication management clinical decision support tool (CDST), to a cohort of similar non-tested patients.

Methods:

An observational study compared a prospective cohort of patients ≥65 years subjected to pharmacogenetic testing to a propensity score (PS) matched historical cohort of untested patients in a claims database. Patients had a prescribed medication or dose change of at least one of 61 oral drugs or combinations of ≥3 drugs at enrollment. Four-month HRU outcomes examined included hospitalizations, emergency department (ED) and outpatient visits and provider acceptance of test recommendations. Costs were estimated using national data sources.

Results:

There were 205 tested patients PS matched to 820 untested patients. Hospitalization rate was 9.8% in the tested group vs 16.1% in the untested group (RR = 0.61, 95% CI = 0.39–0.95, $p = 0.027$), ED visit rate was 4.4% in the tested group vs 15.4% in the untested group (RR = 0.29, 95% CI = 0.15–0.55, $p = 0.0002$) and outpatient visit rate was 71.7% in the tested group vs 36.5% in the untested group (RR = 1.97, 95% CI = 1.74–2.23, $p < 0.0001$). The rate of overall HRU was 72.2% in the tested group vs 49.0% in the untested group (RR = 1.47, 95% CI = 1.32–1.64, $p < 0.0001$). Potential cost savings were estimated at $218 (mean) in the tested group. The provider majority (95%) considered the test helpful and 46% followed CDST provided recommendations.

Conclusion:

Patients CYP DNA tested and treated according to the personalized prescribing system had a significant decrease in hospitalizations and emergency department visits, resulting in potential cost savings. Providers had a high satisfaction rate with the clinical utility of the system and followed recommendations when appropriate.

Background

Pharmacogenetic testing is available to guide prescription drug treatment decisions, such as which drug or dose to use for specific patients based on their genotype. Testing is increasingly becoming the new standard of care for a variety of drugs used to treat different disease states. The Clinical Pharmacogenetic

Implementation Consortium (CPIC)[1] has published 35 Dosing Guidelines which provide guidance for clinicians when genotype information is available. The FDA required labeling of clopidogrel (Plavix®) contains a boxed warning describing the role of 'loss of function variants' in the genes coding for cytochrome P450 (*CYP2C19*) that reduce drug activation and corresponding anti-platelet activity[2]. CPIC guidelines for *CYP2C19* provide guidance on prescribing of *P2Y12* antagonists based on the results of *CYP2C19* testing, if available, for acute coronary syndrome patients undergoing percutaneous intervention[3]. Similar examples for common medications with CPIC genotype guided prescribing include tricyclic antidepressants, selective serotonin reuptake inhibitors, and simvastatin[4–6]. On a broader scale, pharmacogenetic testing for CYPs has the ability to maximize drug treatment effectiveness while reducing risk of adverse effects because the polymorphic CYPs metabolize a majority of the most commonly prescribed medications[7]. In addition, CYP genotypes determine decreased or increased metabolism activity in the majority of patients[8].

Knowledge of CYP genotypes and interactions provides clinically useful information for optimizing polypharmacy regimens for chronically ill, multi-morbid patients[7,9].

Polypharmacy carries a high risk of adverse drug events[10,11] (ADE) as a result of drug–drug interactions (DDI) which are routinely assessed in clinical practice; and drug–gene (DGI) and drug–drug–gene interactions (DDGI), which are not routinely assessed. A recent study of cumulative interaction risk showed that DGIs and DDGIs comprise 15% and 19% of significant interaction risk[12], with the remaining 66% being binary and multi-drug DDIs. According to the FDA, DGIs between genetically poor drug metabolizing enzymes (DME) and their substrate drugs produce drug level changes equivalent to the most extreme change a strong inhibitor of that enzyme would produce[13]. An example of a DDGI is a patient with a loss of function allele (DGI) affecting the metabolism of one of the drugs they are taking and then adding a second concomitant CYP inhibiting drug. These cumulative interactions can phenoconvert patients from normal or intermediate to poor metabolizers of affected drugs and are especially important because of the occurrence of intermediate metabolizers of the most important CYPs in approximately one-third of patients[14]. As a result, DGIs and DDGIs are generally under-recognized and their importance and impact under-estimated in clinical practice. This problem is particularly acute in elderly patients subjected to polypharmacy and leads to a higher risk of adverse events, such as overdose toxicity and prescription drug-treatment failure[15]. These added risks likely result in higher healthcare resource utilization (HRU) and overall costs. One way to reduce the adverse impacts of polypharmacy on increased HRU is to identify DDIs, DGIs, and DDGIs, calculate their cumulative effects, and modify drug regimens accordingly. The clinical decision support tool (CDST) used in this study considers cumulative drug and gene interactions[16,17] predicting the magnitude of drug level increase or decrease that is often greater than any single interaction. Currently, there is limited information on the clinical utility of pharmacogenetic testing and the extent to which physicians act on the results of such tests[18,19].

This paper reports the interim-analysis of a prospective registry study comparing HRU among patients in the YouScript IMPACT (Improving Medication Protocols and Abating Cost of Treatment) registry who were tested to determine their genetics-based CYP metabolizer status, to a historical cohort of untested patients at 4-month follow-up. The prospective registry collected information about elderly patients at risk for deleterious medication interactions who were tested for pharmacogenetics followed by development of their cumulative DDI, DGI, and DDGI risk profiles by CDST based on their medication regimens. The personalized prescribing CDST's system that was applied in the prospective arm of the study[20] includes use of genetic test results for variants of cytochrome P450s: *CYP2D6*, *CYP2C9*, *CYP2C19*, *CYP3A4*, and *CYP3A5*, and warfarin receptor gene *VKORC1*, combined with known drug–drug interactions[12]. Recommendations to prescribers by specialized pharmacists using the CDST supported medication management decisions. We then estimated the potential financial impact of testing using national standard costs for hospitalizations, emergency department (ED, and outpatient visits. The study also assessed prescriber's attitudes and use of the CDST in supporting clinical decisions.

Methods

All patients included in the tested group provided informed consent to participate in the study. The prospective registry and the study protocol were reviewed and approved by Western Institutional Review Board (IRB) and the retrospective analysis for the historical control was reviewed and approved by the University of Utah IRB.

Study design

This was an observational cohort study that compared HRU in patients prospectively tested with the YouScript® system (tested group) at three clinical sites specializing in cardiology, primary care, and internal medicine matched to a historical cohort of patients that had not undergone pharmacogenetic testing (untested group) identified in the Medical Outcomes Research for Effectiveness and Economics (MORE[2]) Registry, a commercially available administrative claims database. The study period was October 20, 2014 to June 9, 2015

(tested group) and July 1, 2012 to December 31, 2013 (untested group). Additional information on the YouScript system is provided in Appendix B.

Intervention

Tested group

Buccal samples were obtained from eligible patients for determination of genotype and shipped to Genelex Corporation (Seattle, WA). Genelex is accredited by the College of American Pathologists (CAP 1073709); certified under the Clinical Laboratory Improvement Amendments (CLIA No. 50D0980559); is Washington State Medical Test Site No. MTS-60353885; New York State Department of Health license no. PFI 8201; and is licensed to perform high complexity clinical testing in all US states. DNA extractions from buccal swabs were performed using the MagJET genomic DNA extraction kit from Thermo Fisher (Waltham, MA). Genotypes were obtained using a laboratory-developed, multiplex PCR-based tests followed by single base primer extension for variant detection by mass spectrometry (MassArray Analyzer 4 System, Agena Bioscience, San Diego, CA). Variants tested include: *CYP2D6*: *2,*2A,*3-*12,*14,*15,*17,*19,*20,*29,*35,*36,*41, gene deletions and duplications. *CYP2C19*: *2-*10,*12,*17. *CYP2C9*: *2-*6,*8,*11,*13,*15. *CYP3A4*: *22. *CYP3A5*: *3. *VKORC1*: c.-1639G > A. The gene panel was decided upon based on the high frequency of variation and the variety of common medications that it effects. The CYPs selected are the CYPs that have been shown to have a consistent relationship with drug levels. The absence of a positive test result for all variants listed results in the assignment of a *1 wild type status. Patient phenotypes and medication list were analyzed by YouScript and verified by a clinical pharmacist. YouScript is a CDST that performs a comprehensive analysis of patient medication regimen and their genetics using a proprietary algorithm and a curated database of the primary literature to predict changes in drug levels[12]. A report highlighting the cumulative potential DDI, DGI, and DDGI risks with alternative drug treatment suggestions were curated by a clinical pharmacist and the CDST and then sent to the provider (see Appendix C for sample report). Interaction types in order of decreasing severity were: 'change', 'consider', 'monitor', and 'no change'. 'Change' interactions were defined as most severe and generally denote contraindicated drug combinations, duplicate therapy or literature recommendations to avoid (or significantly modify) a particular drug–drug or drug–gene combination, e.g., clopidogrel in *CYP2C19* poor metabolizers. 'Consider' interactions were defined as recommendations to consider changing or adjusting the dose of one or more of the current medications based on documented clinical literature and/or known pharmacokinetic properties. 'Monitor' interactions were defined as recommendations to monitor closely for decreased effectiveness and/or adverse effects specific to these drugs, as the patient may be at increased risk. 'No change' interactions were when no change in medications or dose were expected.

Data source

Untested group

The MORE^2 Registry was used to identify patients for the untested group. The MORE^2 Registry is a large nationally representative and de-identified administrative claims database that includes longitudinal patient-level data from a broad range of data sources across all payer types (Commercial, Medicare, Managed Medicaid, and Miscellaneous), geographic regions (98.2% of US counties and Puerto Rico), healthcare settings (inpatient and outpatient services), and provider specialties. The MORE^2 data warehouse contains data pertaining to more than 9.7 billion medical events for more than 123 million members, 769,000 physicians, and 261,000 clinical facilities. Patient-level data includes age, gender, race or ethnicity, and comprehensive information on disease diagnoses, chronic conditions, and medical and pharmacy use[21].

Study population

Untested group

The untested group consisted of patients ≥65 years who were continuously enrolled in the MORE^2 Registry between January 1, 2012 and December 31, 2013, and had a first claim or change in dose for one or more oral forms of 55 single ingredient and six medication combinations between July 1, 2012 and March 31, 2013 (Table 1). The listed medications were chosen based on the potential for significant DGI risk identified by *in vivo* pharmacokinetic or pharmacodynamic evidence, by FDA label, or dosing guidance such as available from CPIC[1]. The date of the first claim or dose change was assigned as the index date. In addition, patients treated with three or more medications[10] including at least one from the list in Table 1 on index date were included to further mimic the prospective cohort. Table 1 lists the drugs deemed high-risk that were considered in the inclusion criteria for both the tested and untested groups.

Tested group

This group only included patients who were aged ≥65 years at the time of study enrollment (index date) and initiated therapy or had a dose change for at least one oral medication from Table 1 within 120 days prior to study enrollment, and were receiving three or more medications, including at least one from Table 1.

Table 1. High-risk CYP450 medications and the major CYP450 genetic variants affecting metabolism of these medications.

Generic (CYP450)	Generic (CYP450)	Generic (CYP450)
Amitriptyline (CYP2D6, CYP2C19)	Fluoxetine (CYP2D6, CYP2C19)	Pimozide (CYP2D6)
Aripiprazole (CYP2D6)	Flurbiprofen (CYP2C9)	Piroxicam (CYP2C9)
Atomoxetine (CYP2D6)	Fluvoxamine (CYP2D6)	Proguanil (CYP2C19)
Carvedilol (CYP2D6)	Haloperidol (CYP2D6)	Propafenone (CYP2D6)
Celecoxib (CYP2C9)	Hydrocodone (CYP2D6)	Propranolol (CYP2D6)
Citalopram (CYP2C19)	Ibuprofen (CYP2C9)	Risperidone (CYP2D6)
Clobazam (CYP2C19)	Iloperidone (CYP2D6)	Sertraline (CYP2C19)
Clomipramine (CYP2D6)	Imipramine (CYP2D6, CYP2C19)	Tetrabenazine (CYP2D6)
Clopidogrel (CYP2C19)	Indomethacin (CYP2C9)	Thioridazine (CYP2D6)
Clozapine (CYP2D6)	Meloxicam (CYP2C9)	Timolol (CYP2D6)
Codeine (CYP2D6)	Metoprolol (CYP2D6)	Tolterodine (CYP2D6)
Desipramine (CYP2D6)	Mexiletine (CYP2D6)	Torsemide (CYP2C9)
Dextromethorphan (CYP2D6)	Nortriptyline (CYP2D6)	Tramadol (CYP2D6)
Diazepam (CYP2C19)	Omeprazole (CYP2C19)	Trimipramine (CYP2D6)
Doxepin (CYP2D6, CYP2C19)	Oxycodone (CYP2D6)	Venlafaxine (CYP2D6
Escitalopram (CYP2C19)	Paroxetine (CYP2D6)	Voriconazole (CYP2C19)
Esomeprazole (CYP2C19)	Perphenazine (CYP2D6)	Vortioxetine (CYP2D6)
Fesoterodine (CYP2D6)	Phenobarbital (CYP2C9, CYP2C19)	Chlorpheniramine/hydrocodone (CYP2D6)
Flecainide (CYP2D6)	Phenytoin (CYP2C9, CYP2C19)	Acetaminophen/codeine (CYP2D6)
Acetaminophen/oxycodone (CYP2D6)	Acetaminophen/tramadol (CYP2D6)	
acetaminophen/hydrocodone (CYP2D6)	Dextromethorphan/guaifenesin (CYP2D6)	

Exclusion criteria were similar for the tested and untested groups and included patients who previously had pharmacogenetic testing (CPT codes 81225, 81226, 81227); a diagnosis of current malabsorption syndrome (ICD-9 codes 579.0, 579.3, 579.8, and 579.9); currently hospitalized; receiving treatment or diagnosed with cancer (140.x–209.x and 235.0x–239.x); current diagnosis of malnourishment (263.x); a history of organ transplant; or receiving IV antibiotics or immunosuppressant medications. Exclusion criteria were assessed prior to enrollment. In the tested group, no subjects had cancer or a diagnosis of malabsorption. To make the historical control comparable, those who had cancer or malabsorption were excluded.

Study outcomes

The primary outcome was HRU at 4 months post-enrollment. HRU included inpatient (hospitalization), outpatient (physician office) services, and ED visits. The secondary outcome was provider's perception of clinical utility of pharmacogenetic testing and the YouScript CDST in supporting prescription drug treatment decisions. The potential cost impact of testing was evaluated by applying standardized costs from national sources to the different rates of resources used by the tested and untested groups.

Assessing HRU

Untested group

The number and rate of patients with an event (hospitalization, ED visit, or outpatient visit) and mean number of events were calculated as documented in the MORE[2] Registry. Hospitalizations were identified using claims which had at least one hospital revenue code or associated CPT-4 codes (99221–99223, 99231–99233, 99238, 99239, 99251–99255, 99291) and at least one CMS bill type code (011X, 012X, 041X, 084X)[22], all claims (contained within, overlap, consecutive days, or transfers) into one claim segment. The earliest claim date was defined as the admission date and the last claim date as the discharge date. ED visits were defined based on the ED revenue codes and CPT-4 codes (99281–99285). Outpatient visits were based on outpatient revenue codes and CPT-4 codes (99201–99205, 99211–99215, 99241–99245).

Tested group

Clinical data were obtained by abstracting data from patient medical records and test reports, querying patients, and surveying providers. Data were entered into electronic Case Report Forms.

Estimating HRU costs

Costs were estimated using values reported by the National Center for Health Statistics (NCHS), Medical Expenditure Panel Survey (MEPS)[23], and Healthcare Cost and Utilization Project (HCUP)[24]. The 2012 MEPS data was used to determine the annual cost of a hospitalization, ED visit, and outpatient visit for patients ≥65 years. The MEPS reported a median annual hospitalization cost as $12,996 ($19,604 mean), median annual ED visit cost as $684 ($1285 mean)[23], and a median annual office visit cost as $1006 ($2278 mean)[23]. For this study, the MEPS reported hospitalization and ED visit costs were

assumed to be for a single event. However, the MEPS reported annual cost for office visits was assumed to be for multiple visits. Therefore, to estimate the cost of a single office visit, the annual office visit cost was divided by 6.7, which was the rate of annual outpatient visits reported in National Ambulatory Medical Care Survey 2010 Summary Tables[25], providing a median rate of $150 (mean rate = $340) per outpatient visit used for this calculation.

Statistical analysis

Treatment group characteristics were calculated and compared using descriptive statistics. A propensity score (PS) matching technique was used[26,27] to address confounding and selection bias due to the different sample sizes. The PS is a measure of the probability of treatment assignment (being in the tested group) that was conditional on observed baseline covariates. Matching by PS addresses balance in the tested group for baseline covariates that may influence both treatment selection and treatment outcomes. The covariates used for matching included patient baseline age, gender, D'Hoore-Charlson comorbidity index score (CCI)[28], for specific morbidities including congestive heart failure, chronic obstructive pulmonary disease, cerebrovascular disease, diabetes, diabetes with complications, dementia, hemiplegia or paraplegia, mild liver disease, myocardial infarction, peripheral vascular disease, moderate or severe renal disease, rheumatologic disease, moderate or severe liver disease, and peptic ulcer disease. In addition, the matching process also controlled for medications listed in Table 1. Race and insurance type were not used in PS matching due to the dominance of white patients and lack of insurance information in the tested group. The 'nearest' neighbor-matching algorithm was used to ensure that tested patients would have four matched untested counterparts.

Results

A total of 82,073 untested patients from the Inovalon MORE^2 database were compared to the 205 tested patients (Figure 1) to obtain the 820 untested patients used as PS matched controls.

Table 2 reports patient demographics for tested and untested groups before and after PS matching. Before matching, the tested cohort was older, had more male patients and lower CCI scores vs the untested group. Statistically significant differences were seen among certain comorbidities (higher rates of congestive heart failure, diabetes and its complications, and myocardial infarction; and lower rates of diabetes in the untested group compared to the tested group). Medication use at baseline was higher for the tested group for the following drugs: carvedilol, celecoxib, citalopram, clopidogrel, diazepam, escitalopram, hydrocodone, meloxicam, metoprolol, omeprazole, paroxetine, sertraline, and venlafaxine. After PS matching, all statistically significant differences reported before matching were balanced between the two groups determined by an absolute standardized difference of less than 0.1 (Figure 2). The standardized differences before matching (stars) had wider distribution compared to after matching (dots), indicating narrower variable distribution resulting from the matching process.

Table 3 compares HRU by testing status; Overall HRU was observed in 72.2% of patients in the tested group vs 49.0% of patients in the untested group (RR = 1.47, 95% CI = 1.32–1.64, $p < 0.0001$); hospitalization rate was 9.8% in the tested group vs 16.1% in the untested group (RR = 0.61, 95% CI = 0.39–0.95, $p = 0.027$); ED visits were 4.4% in the tested group vs 15.4% in the untested group (RR = 0.29, 95% CI = 0.15–0.55, $p = 0.0002$); and outpatient visits were 71.7% in the tested group vs 36.5% in the untested group (RR = 1.97, 95% CI = 1.74–2.23, $p < 0.0001$).

The mean number of total HRU was 2.2 in the tested group vs 2.7 in the untested group (RR = 0.82, 95% CI = 0.66–1.02, $p = 0.0751$). Mean number of hospitalizations was 0.1 for the tested group and 0.5 for the untested group (RR = 0.25, 95% CI = 0.15–0.42, $p < 0.0001$); however, hospitalization in the untested group also included long-term care rehabilitation. The mean number of outpatient visits were 2.0 for the tested group and 1.9 for the untested group (RR = 1.03, 95% CI = 0.83–1.28, $p = 0.7814$); and the mean number of ED visits were 0.1 for the tested group and 0.2 for the untested group (RR = 0.23, 95% CI = 0.11–0.46, $p < 0.0001$).

Table 4 represents the estimated cost implications of genetic testing. In the untested matched cohort, 13 more patients had a hospitalization than in the tested group during the 4-month follow-up period. At $12,992 median cost (mean = $19,604) per hospitalization in the elderly according to the MEPS report[23], the difference in the hospitalization cost was $168,896 ($254,852 using mean cost). For ED visits there was a differential excess of 23 patients in the untested group, at a median cost of $684 per visit (mean = $1285)[23] for a total of $15,390 difference in cost ($28,913 using mean cost). At the same time, the total number of outpatient visits in the tested group increased by 152, with a median cost estimate of $150 per visit (mean = $340)[25], adding $22,819 in costs ($51,672 using mean cost). When all components of HRU are considered, $788 of the list price of $914 for the pharmacogenetic test (2015 CMS Clinical Laboratory Fee Schedule) is offset by HRU avoided due to testing. Using mean costs instead of the median cost yields a cost reduction of $1132 from HRUs avoided in the tested group and a net savings of $218 per patient, including the cost of the test.

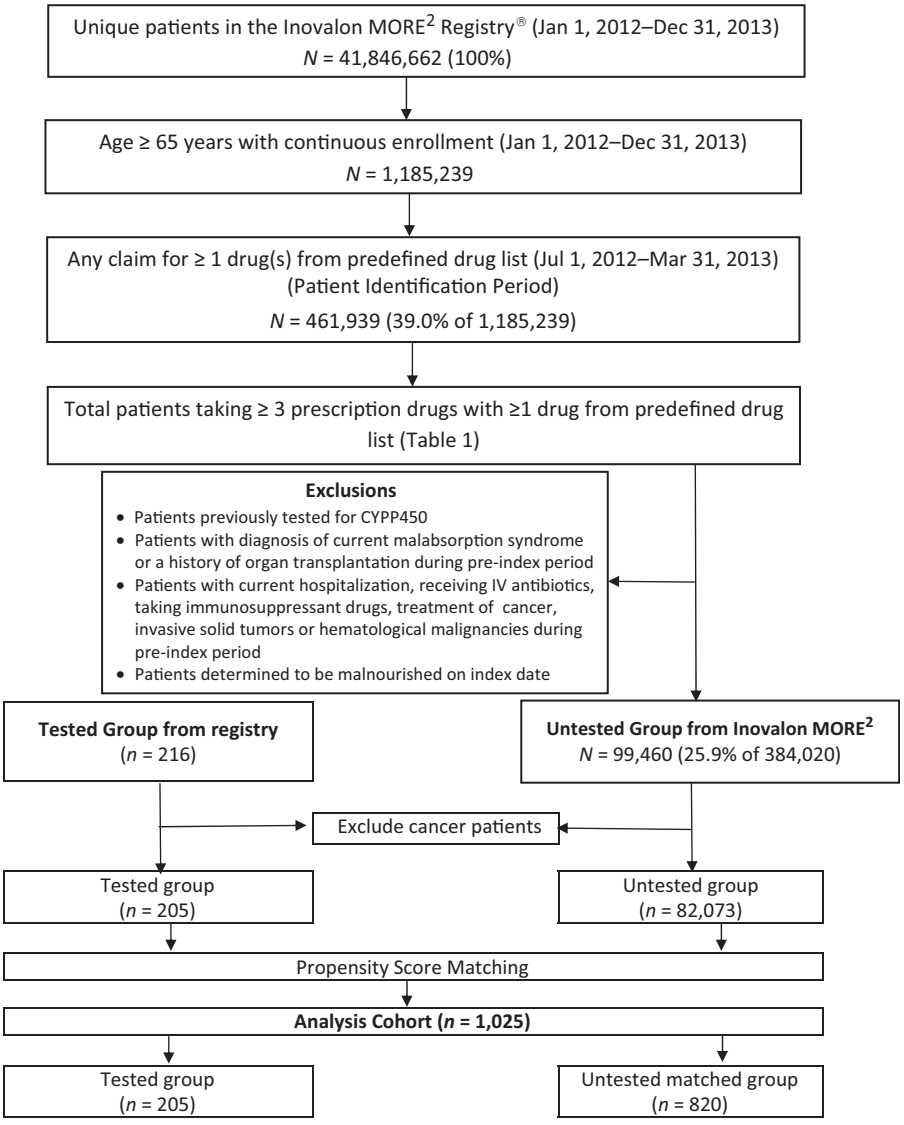

Figure 1. Patient selection flow chart.

Table 5 reports physician attitudes to the recommendations provided to them as a result of testing and included 'change', 'consider', or 'monitor'. On average there were approximately two recommendations per patient during the 4-month trial due to multiple recommendations for some patients. For the 205 patients in the tested group, a total of 381 recommendations were made for prescribed medications listed in Table 1. The percentage of physicians following these recommendations varied from 43% in the 'change' category to 83% for 'monitor'; and, overall, the physicians followed 46% of the test recommendations. Reasons for physicians not following recommendations included patient tolerance (49%) and already monitoring (41%). According to Table 6, more than 95% of physicians considered YouScript helpful for clinical decision-making, mainly because it identified previously unrecognized drug–gene or drug–drug interactions.

Discussion

Assessing the clinical and economic value of pharmacogenetic testing for reimbursement has been described as challenging because research methods applied to traditional medicines have to adapt in order to evaluate the scope and complexity of personalized medicine[29]. Yet the requirement of clinical evidence and value is beginning to favor reimbursement for testing[30].

The focus of our study was to assess the impact on HRU of pharmacogenetic testing of elderly polypharmacy patients exposed to one of the 55 drugs, and the six most common combinations thereof, that have been known to have drug–gene interactions which may result in adverse clinical consequences. In order to identify a population that is likely to have a high frequency of potential interactions with the CYPs, we only included patients taking

Table 2. Characteristics of the study patients before and after propensity score matching ($n = 82,278$)†.

Variable	Before matching						After matching			
	Tested ($n = 205$)		Untested ($n = 82,073$)		*p*-value‡	Standardized difference	Untested ($n = 820$)		*p*-value‡	Standardized difference
	n/Mean	%/SD	*n*/Mean	%/SD			*n*/Mean	%/SD		
Age, Mean (SD)	75	6.9	74	6.0	<0.0001	0.16	75	6.5	0.3239	−0.08
Gender (Male), *n* (%)	87	42.4	31,762	38.7	<0.0001	0.08	371	45.2	0.4700	0.06
D'Hoore Comorbidities										
CCI, Mean (SD)	0.8	1.0	1.5	1.9	<0.0001	−0.52	0.8	1.1	0.6337	−0.06
Congestive Heart Failure, *n* (%)	5	2.4	6841	8.3	0.0009	−0.26	30	3.7	0.3898	−0.07
Diabetes + complications, *n* (%)	7	3.4	8318	10.1	0.0007	−0.27	20	2.4	0.4353	0.06
Diabetes, *n* (%)	37	18.0	27,912	34.0	<0.0001	−0.37	148	18.0	0.9999	0.00
Myocardial Infarction, *n* (%)	1	0.5	3618	4.4	0.0018	−0.26	7	0.9	0.5944	−0.04
Moderate or severe renal disease, *n* (%)	4	2.0	9530	11.6	<0.0001	−0.39	16	2.0	0.9999	0.00
Medications taken by patients at baseline										
Carvedilol (Coreg), *n* (%)	38	18.5	4557	5.6	<0.0001	0.41	161	19.6	0.7223	−0.03
Celecoxib (Celebrex), *n* (%)	13	6.3	1623	2.0	0.0003	0.22	54	6.6	0.8994	−0.01
Citalopram (Celexa), *n* (%)	19	9.3	2538	3.1	<0.0001	0.26	88	10.7	0.5399	−0.05
Clopidogrel (Plavix), *n* (%)	24	11.7	4448	5.4	0.0005	0.23	108	13.2	0.5758	−0.04
Diazepam (Valium), *n* (%)	11	5.4	1150	1.4	0.0002	0.22	38	4.6	0.6605	0.03
Escitalopram (Lexapro), *n* (%)	8	3.9	1242	1.5	0.0137	0.15	45	5.5	0.3592	−0.08
Hydrocodone (Zohydro), *n* (%)	20	9.8	12,136	14.8	0.0479	−0.15	89	10.9	0.6484	−0.04
Meloxicam (Mobic), *n* (%)	43	21.0	4914	6.0	<0.0001	0.45	142	17.3	0.2231	0.09
Metoprolol (Toprol-XL), *n* (%)	54	26.3	13,971	17.0	0.0008	0.23	210	25.6	0.8303	0.02
Omeprazole (Prilosec), *n* (%)	65	31.7	14,274	17.4	<0.0001	0.34	260	31.7	0.9999	0.00
Paroxetine (Paxil), *n* (%)	16	7.8	1212	1.5	<0.0001	0.30	57	7.0	0.6708	0.03
Sertraline (Zoloft), *n* (%)	18	8.8	2933	3.6	0.0005	0.22	85	10.4	0.4995	−0.05
Venlafaxine (Effexor), *n* (%)	9	4.4	858	1.0	0.0004	0.21	27	3.3	0.4451	0.06

†Only variables with significant differences before matching are presented. For a full list of variables included in matching, refer to Appendix 1.
‡*T*-test *p*-values for age and gender, chi-square/Fisher Exact test *p*-values for other categorical variable where appropriate.
SD, Standard Deviation.

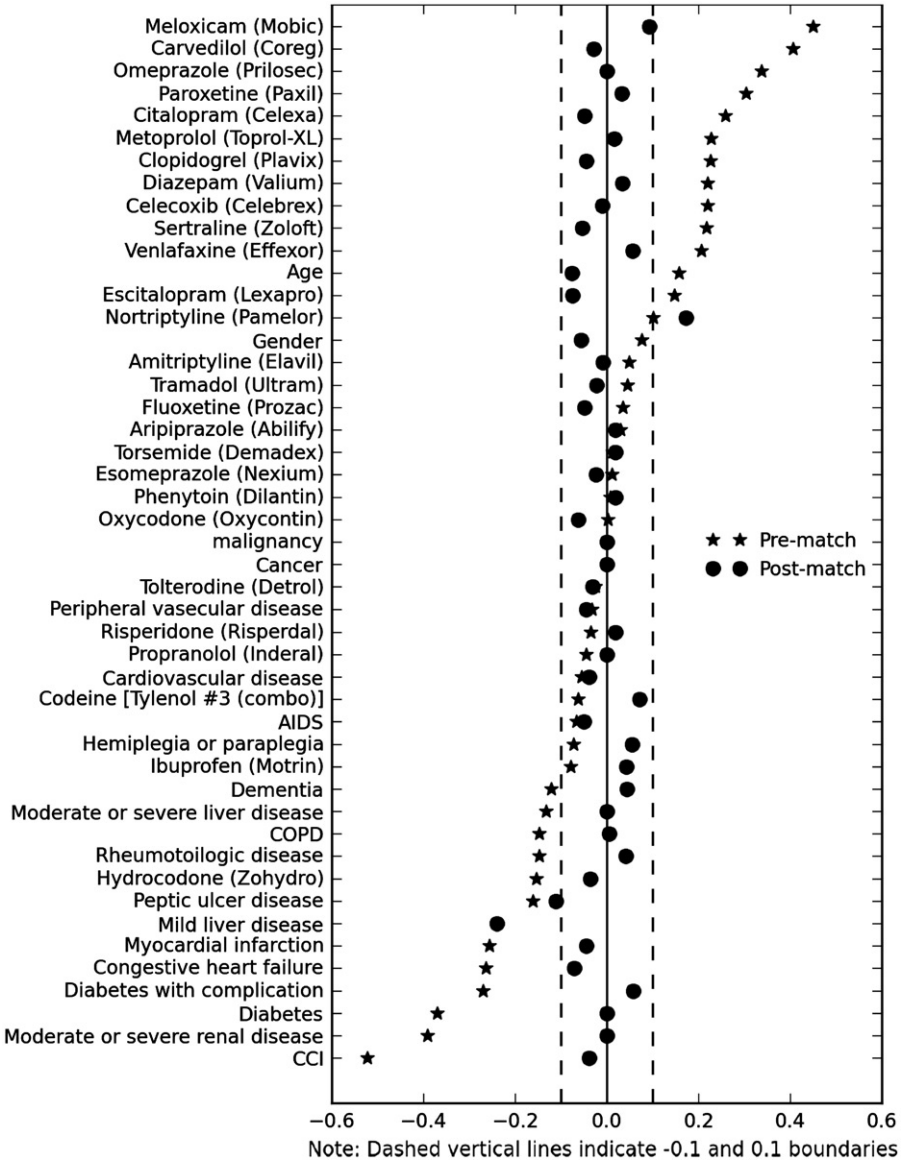

Figure 2. Distribution of standardized differences before and after propensity score matching.

Table 3. Healthcare resource utilization in the study population during 4-month follow-up period.

Outcome	Adjusted (propensity score matched)				
	Tested ($n = 205$)	Untested ($n = 820$)	IRR or RR	95% CI	*p*-value
Hospitalization					
Patients having, *n* (%)	20 (9.8%)	132 (16.1%)	0.61	0.39–0.95	0.0273
Number of hospitalizations, Mean (SD)	0.1 (0.4)	0.5 (1.6)	0.25	0.15–0.42	<0.0001
Outpatient visits					
Patients having, *n* (%)	147 (71.7%)	299 (36.5%)	1.97	1.74–2.23	<0.0001
Number of outpatient visits, Mean (SD)	2.0 (2.6)	1.9 (3.7)	1.03	0.83–1.28	0.7814
ED visits					
Patients having, *n* (%)	9 (4.4%)	126 (15.4%)	0.29	0.15–0.55	0.0002
Number of ED visits, Mean (SD)	0.1 (0.3)	0.2 (0.7)	0.23	0.11–0.46	<0.0001
Total HRU					
Patients having, *n* (%)	148 (72.2%)	402 (49.0%)	1.47	1.32–1.64	<0.0001
Number of HRU, Mean (SD)	2.2 (2.9)	2.7 (4.5)	0.82	0.66–1.02	0.0751

SD, standard deviation; IRR, Incident rate ratio from Poisson regression models; RR, Relative risk from Poisson regression models with robust error variance.

Table 4. Estimated cost implications of genetic testing using cost estimates from NCHS, MEPS, and HCUP.†.

	Tested ($n = 205$)	Untested ($n = 820$)	Untested (accounting for 4:1 match)	Using median costs			Using mean costs		
				Cost diff.	Resource costs	Per patient	Cost diff.	Resource costs	Per patient
Hospitalization					$12,992			$19,604	
Patients with hospitalizations, *n*	20	132	33	$168,896			$254,852		
ED visit					$684			$1285	
Patients with ED visit, *n*	9	126	32	$15,390			$28,913		
Outpatient visit					$150			$340	
Patients with outpatient visit, *n*	147	299	75						
Number of visits	294		142	($22,819)			($51,672)		
Including hospitalizations, ED and outpatient visits									
Sub-total (cost difference sum for inpatient, ED and outpatient)				$161,467		$788	$232,093		$1132
Cost of testing (205 patients)				($187,370)	$914		($187,370)	$914	
Net cost (cost difference − cost of testing)				($25,903)		($126)	$44,723		$218

†Numbers reported for the untested group accounting for 4:1 match were rounded to the nearest integer. However, unrounded numbers were used to calculate costs. Numbers in bracket indicates negative.

three or more medications. Analysis of the 205 tested subjects showed a 47% increase in overall HRU, an ∼40% decrease in number of hospitalized patients, and a 70% reduction in ED visits compared to the matched historical controls (number of unique patients having the event with some patients having multiple events but only counted once). The overall HRU increase was due to an increase in outpatient visits, most likely driven by the increased need for changes in therapy regimens based on test results. However, analysis of the mean events (mean number of events among the total patient cohort) showed no significant difference in outpatient visits and a non-significant 18% decrease in total HRU, while showing a greater than 75% decrease in inpatient hospitalizations and a 77% decrease in ED visits.

Our hypothetical costs estimates, based on median national data, predicts a saving of $788 per patient, which offsets most of the test cost, resulting in the healthcare system paying a net of $126 or 14% of the retail cost of the test estimated at $914. When mean national data were used, the hypothetical model predicts a $1132 saving, which completely offsets the cost of the test, resulting in a net savings of $218 per patient. Whether median or mean costs are used, the model suggests that the cost of the test is nearly or completely offset by savings resulting from decreased healthcare resource utilization, providing evidence for the robustness of the model.

Since follow-up was limited to 4-months, the potential cost savings would be expected to increase over time given the one-time expense of testing. A recently conducted cost-effectiveness analysis considered a one-time genetic test to avoid lifetime adverse drug reactions[31]. The impact on quality-of-life of decreased hospitalization days was the effectiveness measure and an incremental cost-effectiveness ratio of $53,680 per additional quality adjusted life year (QALY) was determined, well within guidelines in countries where this measure is routinely used for reimbursement decisions.

The role of using pharmacogenetic tests as clinical support tools has been previously reported. A study by Swen *et al.*[32] developed guidelines guiding antidepressant dosing based on pharmacogenetic testing results. Another study reported how pharmacogenetic information can be used to select the ideal non-steroidal anti-inflammatory drug, and potential benefits associated with this practice[33]. Pharmacogenetic testing information can also affect patient safety[19] and drug-related hypersensitivity reactions[34]. Our findings are consistent with evidence to date that has focused on assessing the potential costs savings and adverse events avoided by using pharmacogenetic testing[19,32–34]. A cost analysis done by Johnson *et al.*[35] demonstrated potential savings of $222,426–$444,852 if *CYP2C19* genotyping shifted 10% or 20% of clopidogrel patients to anti-platelet therapy not affected by a lack of activation within a theoretical cohort of 1000 patients.

Table 5. Distribution of physicians following YouScript recommendations ($n = 381$)†.

Recommendation severity	Followed percentage	Followed	Not followed	Reason for not following the recommendation ($n = 207$)			
				Patient tolerating	Monitoring already	Drug transition-temporary	Other‡
Change	43%	35	47	15	23	1	8
Consider	45%	129	158	87	60	1	10
Monitor	83%	10	2	0	2	0	0
Total	46%	174	207	102	85	2	18

†If any type of interaction was reported, the incidence was considered a YouScript recommendation. The three types of interaction are drug–gene, drug–drug, and drug–drug–gene interactions.
‡Other category included: Doctor's decision (10 patients), patient's awareness (two patients), patient declined (two patients), patient taking medications as needed (four patients).

Table 6. Distribution of YouScript helpfulness for clinical decision-making ($n = 205$).

Was YouScript helpful for clinical decision-making?	Count	Percentage
Yes, the patient's drug regimen was changed as a result of YouScript testing	32	15.6
Yes, previously unrecognized drug–gene or drug–drug interactions were identified	138	67.3
Yes, YouScript Personalized Prescribing System was helpful because (Specify below)	25	12.2
No, I did not find YouScript Personalized Prescribing System helpful for clinical decision-making	7	3.4
Not reported	3	1.5
Total	205	100

A more recent study by Winner *et al.*[36] demonstrated significant cost savings for pharmacogenetic-guided therapy in psychiatric patients. Overall, those that were tested incurred $1036 lower medication costs in 1 year, and, specifically, in those where test recommendations were followed, the savings increased to $2775 per year[36].

Alterations in drug levels can lead to increased ED visits and hospital admissions and readmissions due to adverse events or diminished treatment response. ADEs account for more than 700,000 annual ED visits for Medicare patients[37], and 16.6% of hospitalizations in the elderly[38]. Similarly 2–8% of hospital re-admissions for Medicare patients occur due to ADEs, resulting in extremely high and potentially preventable costs[39]. Adverse drug events leading to ED visits are also an important cause of morbidity, particularly among patients $\geq$65 years[40]. A recent Canadian study[41] discussed common drugs that lead to ED visits and hospitalization due to adverse events including opioids, non-steroidal inflammatory drugs, and anticoagulants, all affected by polymorphic DMEs. Colleagues at Vanderbilt have estimated that 383 adverse events could have been avoided within 52,942 medical home patients, exposed to medications similar to those in our study, and with known outcomes influenced by variant alleles by pre-emptive genotyping[7].

Another important component to consider is the effect of pharmacogenetic testing on changing subsequent clinical decisions[42]. Evidence supporting the clinical utility of pharmacogenetic testing and its impact in clinical practice is emerging in multiple disease states. For example, genetic information improves diagnostic evaluation in patients presenting with coronary artery disease symptoms[43]. Another study reported better risk stratification when incorporating pharmacogenetic information into treatment decisions of patients with breast cancer which allowed for patient-tailored therapy[44]. There is an increased trend of adopting pharmacogenetic testing in clinical practice; however, clinical utility and economic value should be properly evaluated before widespread adoption of this CDST[45]. As pharmacogenetic testing becomes more pervasive, the demand for evidence of improved outcomes due to testing will increase in order for health plans to consider reimbursement[46,47]. In our study, providers followed 46% of test recommendations to modify patient medication regimens. Of the recommendations not followed, patients were most commonly described as tolerant to the drug (49%) or already being monitored (41%). Provider satisfaction with the testing system was also high. More than 95% of physicians considered YouScript helpful to clinical decision-making due to the identification of previously unrecognized potentially important medication interactions. A final aspect of genetic profiling is the inherent future clinical utility of having information on record that will contribute to the development of future treatment plans and clinical decisions[42].

Strengths and limitations

In order to provide timely evidence of the impact of testing vs a control group, patients were matched on key variables via a propensity score methodology to a historical control from a national administrative claims database. The large number of historical controls allowed for close matching at a four-to-one ratio of controls to test subjects. This mixed method design allowed us to demonstrate the feasibility of reduction in healthcare resources based on genetic profiling. The results from this analysis can inform the design of future studies, where direct comparisons in a unified database can be made.

Our study has several important limitations. First, despite an innovative method to overcome the challenge of providing closely matched controls for our complex polypharmacy test subjects, the use of an administrative database for historical controls provided inherent potential bias. The subjects selected for the control group were drawn from the most current data-set available to minimize differences in practice changes over time. Propensity score matching was conducted to minimize differences in observed covariates between the two populations. However, PS matching is unable to control for unobserved factors that may affect the outcomes in our study. Race and ethnicity were not included in the propensity score matching, due to limited reporting in the claims data-set. However, a recent report by Van Driest *et al.*[48] noted only a 5% difference in exposure to actionable variants of drug metabolizing enzymes between African–Americans and the general population (96 vs 91%). Despite achieving balance between the groups after matching, there are still expected differences in the prevalence of CYP alleles between major population groups, which were unaccounted for in this analysis.

Second, the registry was based on only a 4-month follow-up, thereby likely under-estimating longer-term cost savings. At 4 months, the cost of genetic testing was almost offset by the savings seen in reduced ED visits and hospital admissions. From the historical control group, both hospitalizations and ED visits nearly doubled from 3 months to 9 months. Extrapolation of the tested group from 4 months out to 1 year to estimate the annual impact would require 1 year follow-up data from tested patients. If the ratio of hospital and emergency department reductions were accompanied by decreased outpatient visits once drug adjustments were made, genetic testing would most likely be cost savings within 1 year. Therefore, the current cost model can be considered a conservative estimate of the impact of CDST guided genetic testing on HRU.

Third, the investigators were not able to distinguish between inpatient visits and rehabilitation visits in mean events. In order to avoid counting rehabilitation visits as hospitalizations, the investigators used patient rates instead of mean events for the cost estimates.

Fourth, only provider satisfaction with the genetic testing results was assessed. The impact of the genetic testing on patient behavior and patient–provider interactions were not determined. A potential consequence of genetic testing on patient behavior may result in greater medication adherence from knowing that adverse events are less likely and that the medication is more likely to achieve the intended results, which may reduce unnecessary health resource utilization. Further, genetic testing may have facilitated discussions between the patient and provider regarding the purpose of the test and education about the medications, leading to increased patient–provider interactions.

Finally, the hypothesis of the benefit of CDST guided genetic testing is, in part, predicated upon the avoidance of adverse drug events. Limited ADEs were reported in the intervention group and ADEs in general are underreported and difficult to identify in an administrative claims database and, thus, we were not able to link the cause of increased HRU in this study. Associations between recommendations followed by physicians and patients were not made at the individual level, because an individual physician may follow some recommendations but not others. Also, the prospective registry did not have information on the number of patients who refused to be enrolled in the study or those who were ineligible for study inclusion.

Conclusions

This study has demonstrated that pharmacogenetic CYP testing of the elderly exposed to polypharmacy, along with appropriate clinical decision support tools, such as YouScript, may provide valuable information to guide prescription drug treatment, reduce hospitalization and ED visits, and lower overall costs. The evidence in this study should be further corroborated with randomized observational data in a unified data source to link these outcomes to the impact of these interventions.

Transparency

Declaration of funding

Genelex provided services consisting of buccal swab collection materials, shipping, genotyping and curation of the YouScript report. Data analysis by the University of Utah was funded through an unrestricted research grant.

Declaration of financial/other relationships

TM and KA are employees and potential equity holders of Genelex. *JME* peer reviewers were paid for their time.

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Appendix A:

Characteristics of study patients before and after propensity score matching ($n = 82,278$).†

Variable	Before matching						After matching			
	Tested ($n = 205$)		Untested ($n = 82,073$)		*p*-value‡	Standardized difference	Untested ($n = 820$)		*p*-value‡	Standardized difference
	n/Mean	%/SD	*n*/Mean	%/SD			*n*/Mean	%/SD		
Age, Mean (SD)	75	6.9	74	6.0	<0.0001	0.16	75	6.5	0.3239	−0.08
Gender										
Male, *n* (%)	87	42.4	31,762	38.7	<0.0001	0.07	371	45.2	0.4700	0.06
Female, *n* (%)	118	57.6	50,311	61.3	<0.0001	−0.07	449	54.8	0.4700	−0.06
D'Hoore Comorbidities										
CCI, Mean (SD)	0.8	1.0	1.5	1.9	<0.0001	−0.52	0.8	1.1	0.6337	−0.06
AIDS, *n* (%)	0	0	179	0.2	NA	−0.07	1	0.1	NA	−0.05
Metastatic solid tumor, *n* (%)	0	0	0	0	NA		0	0	NA	NA
Congestive Heart Failure, *n* (%)	5	2.4	6841	8.3	0.0009	−0.26	30	3.7	0.3898	−0.07
Chronic obstructive pulmonary disease, *n* (%)	12	5.9	8028	9.8	0.0592	−0.15	47	5.7	0.9465	0.01
Cerebrovascular disease, *n* (%)	10	4.9	5039	6.1	0.5596	−0.06	47	5.7	0.6333	−0.04
Diabetes + complications, *n* (%)	7	3.4	8318	10.1	0.0007	−0.27	20	2.4	0.4353	0.06
Dementia, *n* (%)	3	1.5	2706	3.3	0.1698	−0.12	8	1.0	0.5443	0.04
Diabetes, *n* (%)	37	18.0	27,912	34.0	<0.0001	−0.37	148	18.0	0.9999	0.00
Hemiplegia or paraplegia, *n* (%)	6	2.9	3501	4.3	0.4855	−0.07	17	2.1	0.4604	0.05
Mild liver disease, *n* (%)	0	0	2301	2.8	NA	−0.24	23	2.8	NA	−0.24
Malignancy, *n* (%)	0	0	0	0	NA		0	0	NA	NA
Myocardial Infarction, *n* (%)	1	0.5	3618	4.4	0.0018	−0.26	7	0.9	0.5944	−0.04
Peripheral vascular disease, *n* (%)	50	24.4	21,148	25.8	0.6899	−0.03	216	26.3	0.5687	−0.04
Moderate or severe renal disease, *n* (%)	4	2.0	9530	11.6	<0.0001	−0.39	16	2.0	0.9999	0.00
Rheumatologic disease, *n* (%)	2	1.0	2494	3.0	0.0996	−0.15	5	0.6	0.5694	0.04
Moderate or severe liver disease, *n* (%)	0	0	715	0.9	NA	−0.13	0	0	NA	NA
Peptic ulcer disease, *n* (%)	0	0	1058	1.3	NA	−0.16	5	0.6	NA	−0.11
Medications taken by patients at baseline										
Amitriptyline (Elavil), *n* (%)	4	2.0	1094	1.3	0.3568	0.05	17	2.1	0.9122	−0.01
Aripiprazole (Abilify), *n* (%)	1	0.5	243	0.3	0.4564	0.03	3	0.4	0.8022	0.02
Carvedilol (Coreg), *n* (%)	38	18.5	4557	5.6	<0.0001	0.41	161	19.6	0.7223	−0.03
Celecoxib (Celebrex), *n* (%)	13	6.3	1623	2.0	0.0003	0.22	54	6.6	0.8994	−0.01
Citalopram (Celexa), *n* (%)	19	9.3	2538	3.1	<0.0001	0.26	88	10.7	0.5399	−0.05
Clopidogrel (Plavix), *n* (%)	24	11.7	4448	5.4	0.0005	0.23	108	13.2	0.5758	−0.04
Codeine [Tylenol #3 (combo)], *n* (%)	6	2.9	3349	4.1	0.5927	−0.06	15	1.8	0.3211	0.07
Diazepam (Valium), *n* (%)	11	5.4	1150	1.4	0.0002	0.22	38	4.6	0.6605	0.03
Escitalopram (Lexapro), *n* (%)	8	3.9	1242	1.5	0.0137	0.15	45	5.5	0.3592	−0.08
Esomeprazole (Nexium), *n* (%)	5	2.4	1855	2.3	0.8115	0.01	23	2.8	0.7738	−0.02
Fluoxetine (Prozac), *n* (%)	4	2.0	1231	1.5	0.5555	0.03	22	2.7	0.5512	−0.05
Hydrocodone (Zohydro), *n* (%)	20	9.8	12,136	14.8	0.0479	−0.15	89	10.9	0.6484	−0.04
Ibuprofen (Motrin), *n* (%)	12	5.9	6441	7.8	0.3613	−0.08	40	4.9	0.5691	0.04
Meloxicam (Mobic), *n* (%)	43	21.0	4914	6.0	<0.0001	0.45	142	17.3	0.2231	0.09
Metoprolol (Toprol-XL), *n* (%)	54	26.3	13,971	17.0	0.0008	0.23	210	25.6	0.8303	0.02
Nortriptyline (Pamelor), *n* (%)	3	1.5	387	0.5	0.0745	0.10	0	0	NA	0.17

Omeprazole (Prilosec), *n* (%)	65	31.7	14,274	17.4	<0.0001	0.34	260	31.7	0.9999	0.00
Oxycodone (Oxycontin), *n* (%)	13	6.3	5138	6.3	0.8854	0.00	65	7.9	0.4439	−0.06
Paroxetine (Paxil), *n* (%)	16	7.8	1212	1.5	<0.0001	0.30	57	7.0	0.6708	0.03
Phenytoin (Dilantin), *n* (%)	1	0.5	357	0.4	0.5914	0.01	3	0.4	0.8022	0.02
Propranolol (Inderal), *n* (%)	1	0.5	703	0.9	0.9999	−0.05	4	0.5	0.9999	0.00
Risperidone (Risperdal), *n* (%)	1	0.5	623	0.8	0.9999	−0.03	3	0.4	0.8022	0.02
Sertraline (Zoloft), *n* (%)	18	8.8	2933	3.6	0.0005	0.22	85	10.4	0.4995	−0.05
Tolterodine (Detrol), *n* (%)	1	0.5	551	0.7	0.9999	−0.02	6	0.7	0.7045	−0.03
Torsemide (Demadex), *n* (%)	1	0.5	332	0.4	0.5650	0.01	3	0.4	0.8022	0.02
Tramadol (Ultram), *n* (%)	26	12.7	9208	11.2	0.5056	0.05	110	13.4	0.7824	−0.02
Venlafaxine (Effexor), *n* (%)	9	4.4	858	1.0	0.0004	0.21	27	3.3	0.4451	0.06

†Patients who had cancer diagnosis (ICD-9140.x–09.x and 235.0x–239.x) from both cohorts were excluded. The tested group has one metastatic and 10 non-metastatic cancer patients, while the untested group has 710 metastatic and 16,677 non-metastatic cancer patients.

‡*T*-test *p*-values for age and gender, chi-square/Fisher Exact test *p*-values for other categorical variable where appropriate. SD, Standard Deviation.

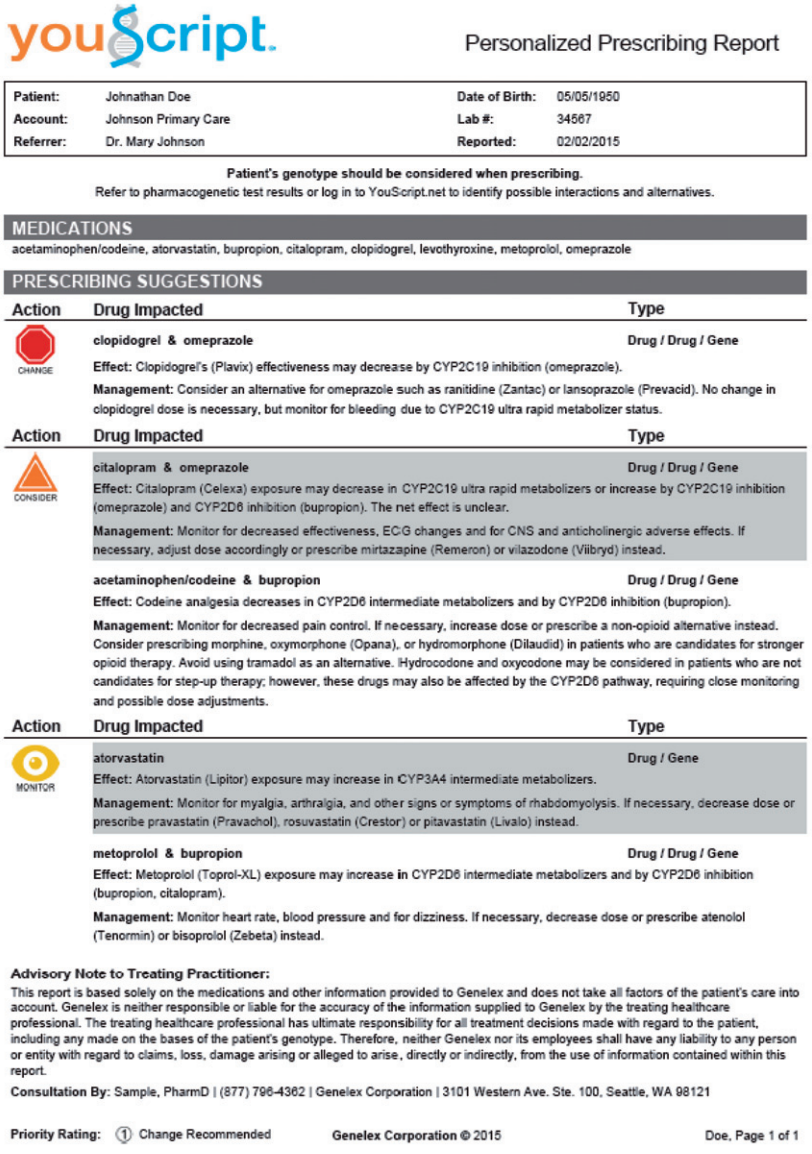
Appendix B: Description of the YouScript system

YouScript is a clinical decision support (CDS) algorithm used to calculate the cumulative effects of multiple interactions between prescription drugs, over the counter medications, herbal preparations, and pharmacogenomics (PGX) data when available. The CDS predicts area under the curve (AUC) changing pharmacokinetic interactions from known metabolic data such as the (Ki) of DME inhibiting and inducing drugs and percentage metabolism of drug substrates by affected enzymes. The pharmacokinetic interactions considered by the algorithm include alterations to absorption, distribution, metabolism, and excretion. Metabolism and excretion include phase 1 reactions by cytochrome P450s, esterases, and others, phase 2 reactions considered include glucuronidation and sulfation. Biochemical interference with transporters such as the ATP-binding cassette and solute carrier transporters are also taken into account. PGX effects on pharmacokinetics include those caused by CYP2D6, CYP2C9, CYP2C19 and many other DMEs.

A list of 2500 medications and other factors that affect patient drug levels is available for query. Patient reports are produced based on patient drug list by accessing a database of 10,300 advisory notes that include links to the 18,000 professionally curated pharmacokinetics, pharmacodynamics, and pharmacogenetics publications that form the YouScript knowledge base. Reports identify patients for whom genetic testing could produce clinically actionable information, provide suggestions for the alteration of drug regimens, and provide lists of alternative medications by therapeutic class.

A more robust description of the algorithm is available from the relevant US patents[49,50]. Drug dosage or hepatic or kidney function are not currently taken into account by the algorithm.

Appendix C: Example of the personalized prescribing report generated by the YouScript system



youScript.

Personalized Prescribing Report

Patient:	Johnathan Doe	**Date of Birth:**	05/05/1950
Account:	Johnson Primary Care	**Lab #:**	34567
Referrer:	Dr. Mary Johnson	**Reported:**	02/02/2015

Patient's genotype should be considered when prescribing.
Refer to pharmacogenetic test results or log in to YouScript.net to identify possible interactions and alternatives.

MEDICATIONS

acetaminophen/codeine, atorvastatin, bupropion, citalopram, clopidogrel, levothyroxine, metoprolol, omeprazole

PRESCRIBING SUGGESTIONS

Action	Drug Impacted	Type
CHANGE	**clopidogrel & omeprazole**	**Drug / Drug / Gene**

Effect: Clopidogrel's (Plavix) effectiveness may decrease by CYP2C19 inhibition (omeprazole).

Management: Consider an alternative for omeprazole such as ranitidine (Zantac) or lansoprazole (Prevacid). No change in clopidogrel dose is necessary, but monitor for bleeding due to CYP2C19 ultra rapid metabolizer status.

Action	Drug Impacted	Type
CONSIDER	**citalopram & omeprazole**	**Drug / Drug / Gene**

Effect: Citalopram (Celexa) exposure may decrease in CYP2C19 ultra rapid metabolizers or increase by CYP2C19 inhibition (omeprazole) and CYP2D6 inhibition (bupropion). The net effect is unclear.

Management: Monitor for decreased effectiveness, ECG changes and for CNS and anticholinergic adverse effects. If necessary, adjust dose accordingly or prescribe mirtazapine (Remeron) or vilazodone (Viibryd) instead.

acetaminophen/codeine & bupropion **Drug / Drug / Gene**

Effect: Codeine analgesia decreases in CYP2D6 intermediate metabolizers and by CYP2D6 inhibition (bupropion).

Management: Monitor for decreased pain control. If necessary, increase dose or prescribe a non-opioid alternative instead. Consider prescribing morphine, oxymorphone (Opana), or hydromorphone (Dilaudid) in patients who are candidates for stronger opioid therapy. Avoid using tramadol as an alternative. Hydrocodone and oxycodone may be considered in patients who are not candidates for step-up therapy; however, these drugs may also be affected by the CYP2D6 pathway, requiring close monitoring and possible dose adjustments.

Action	Drug Impacted	Type
MONITOR	**atorvastatin**	**Drug / Gene**

Effect: Atorvastatin (Lipitor) exposure may increase in CYP3A4 intermediate metabolizers.

Management: Monitor for myalgia, arthralgia, and other signs or symptoms of rhabdomyolysis. If necessary, decrease dose or prescribe pravastatin (Pravachol), rosuvastatin (Crestor) or pitavastatin (Livalo) instead.

metoprolol & bupropion **Drug / Drug / Gene**

Effect: Metoprolol (Toprol-XL) exposure may increase in CYP2D6 intermediate metabolizers and by CYP2D6 inhibition (bupropion, citalopram).

Management: Monitor heart rate, blood pressure and for dizziness. If necessary, decrease dose or prescribe atenolol (Tenormin) or bisoprolol (Zebeta) instead.

Advisory Note to Treating Practitioner:

This report is based solely on the medications and other information provided to Genelex and does not take all factors of the patient's care into account. Genelex is neither responsible or liable for the accuracy of the information supplied to Genelex by the treating healthcare professional. The treating healthcare professional has ultimate responsibility for all treatment decisions made with regard to the patient, including any made on the bases of the patient's genotype. Therefore, neither Genelex nor its employees shall have any liability to any person or entity with regard to claims, loss, damage arising or alleged to arise, directly or indirectly, from the use of information contained within this report.

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