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The INGENIOUS Trial: Impact of pharmacogenetic testing on adverse events in a pragmatic clinical trial

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Abstract

Adverse drug events (ADEs) account for a significant mortality, morbidity, and cost burden. Pharmacogenetic testing has the potential to reduce ADEs and inefficacy. The objective of this INGENIOUS trial (NCT02297126) analysis was to determine whether conducting and reporting pharmacogenetic panel testing impacts ADE frequency. The trial was a pragmatic, randomized controlled clinical trial, adapted as a propensity matched analysis in individuals (N = 2612) receiving a new prescription for one or more of 26 pharmacogenetic-actionable drugs across a community safety-net and academic health system. The intervention was a pharmacogenetic testing panel for 26 drugs with dosage and selection recommendations returned to the health record. The primary outcome was occurrence of ADEs within 1 year, according to modified Common Terminology Criteria for Adverse Events (CTCAE). In the propensity-matched analysis,

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CONFLICT OF INTEREST

The authors have nothing to disclose.

ETHICS DECLARATION

This study was approved by the Institutional Review Board (IRB # 1401206188) of Indiana University School of Medicine.

16.1% of individuals experienced any ADE within 1-year. Serious ADEs (CTCAE level 3) occurred in 3.2% of individuals. When combining all 26 drugs, no significant difference was observed between the pharmacogenetic testing and control arms for any ADE (Odds ratio 0.96, 95% CI: 0.78–1.18), serious ADEs (OR: 0.91, 95% CI: 0.58–1.40), or mortality (OR: 0.60, 95% CI: 0.28–1.21). However, sub-group analyses revealed a reduction in serious ADEs and death in individuals who underwent pharmacogenotyping for aripiprazole and serotonin or serotonin-norepinephrine reuptake inhibitors (OR 0.34, 95% CI: 0.12–0.85). In conclusion, no change in overall ADEs was observed after pharmacogenetic testing. However, limitations incurred during INGENIOUS likely affected the results. Future studies may consider preemptive, rather than reactive, pharmacogenetic panel testing.

Keywords

IGNITE; Adverse Side Effects; Pharmacogenetics

INTRODUCTION

Adverse drug events (ADEs) contribute to the death of approximately 100,000 patients^{1, 2}, and 2 million hospitalizations each year^{3, 4}. ADEs, which are often under-reported⁵, may affect adherence to therapy, reducing drug efficacy and increasing societal disease burden^{6, 7}. Pharmacogenomic testing has the potential to improve patient outcomes and reduce health care system costs. Such benefit could be actualized through the reduction of ADEs and their associated medical costs or through optimization of drug efficacy for expensive health care conditions.

For many commonly used drugs, strong existing evidence links specific genetic variants or alleles to the risk of ADEs or inefficacy. The United States Food and Drug Administration (FDA) has included genetic testing considerations in 338 drug label documents⁸. Guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC), Dutch Pharmacogenomics Working Group (DPWG), and the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) are available which provide expert opinion on drug dosing and selection for drug-gene pairs with very strong evidence supporting the benefit of pharmacogenomic testing^{9–12}. Despite the evidence, pharmacogenomic testing has not been widely adopted in clinical practice. Important implementation studies have been designed to bridge the gap for drug-gene pairs with strong evidence^{13–15}.

A pharmacogenomic test is often considered “actionable” when its result warrants a change in drug selection, dosing, or monitoring for toxicities. The number of actionable drug-gene pairs with level 1 recommendations by CPIC and DPWG now exceeds 70 drugs, although not all are commonly used in practice¹⁰. We considered that the aggregate value of pharmacogenomic testing might be better ascertained by testing the effect of implementation for a wide array of pharmacogenomic variants, rather than a single gene-drug association. We hypothesized that receipt of a CLIA (The Clinical Laboratory Improvement Amendments of 1988) certified genotyping panel targeting 26 widely used drugs would yield significant improvement in clinical outcomes over 1 year. Herein,

we describe the results of the INdiana GENomics Implementation: an Opportunity for the UnderServed (INGENIOUS) trial. The results of and challenges encountered in this multiplexed pragmatic implementation trial are presented.

SUBJECTS AND METHODS

Study Design

The INGENIOUS trial ([NCT02297126](#)) was designed as a pragmatic prospective randomized controlled trial that was powered to evaluate the impact of prospective genotyping on a primary outcome of health care costs during 1 year follow-up¹⁶. The occurrence of ADEs was also a pre-specified outcome of INGENIOUS, which is reported in this manuscript. ADEs were analyzed in a propensity-matched analysis. The study enrolled subjects from 2014 to 2018. This study was approved by the Institutional Review Board (IRB # 1401206188) of Indiana University School of Medicine.

Subjects

Eligible subjects were those over age 18 who received a new “index” prescription for one or more of 26 pharmacogenomic actionable drugs within one of two health systems, an urban safety-net or a large academic health care system. Subjects could not have received the prescription within the preceding 13 months and must have been enrolled in the study within 5 days of the new prescription.

Additionally, subjects in the intervention arm must have: 1) been able and willing to provide consent; 2) received care at their health system more than 365 days prior to enrollment; and 3) been able to provide a blood or saliva sample within 5 days of the index medication. Exclusion criteria included: 1) previous receipt of pharmacogenetic testing and 2) status as an employee or student under the supervision of the investigators.

Subjects receiving a 27th drug (thioguanine) were also eligible for the study, but only one person received thioguanine; this person was randomized to genotyping but not enrolled. The genotyping and enrollment algorithm briefly included drug-gene pair information for a 14th gene (*IFNL3* for interferon therapy) and additional drugs (glyburide, methotrexate, and hydroxychloroquine) which were removed early in the trial due to changing practice patterns or insufficient supporting evidence. Subjects receiving these as index drugs were ineligible for the propensity matched analysis.

Study Procedures and Interventions

The exposure variable of INGENIOUS was clinical pharmacogenomic testing for 26 drug-gene pairs. The overall study flow is summarized in Figure 1A. Enrolled subjects who received a new prescription for one or more of 26 drugs were randomized to standard care or received pharmacogenetic testing for an entire panel containing 43 variants within 13 genes. Individuals randomized to the pharmacogenetic genotype arm were contacted by the study team. Those who consented and provided a biological sample (blood or saliva) within 5 days of the index prescription were included in the genotyped arm. Results of genotyping, as described below, were entered into the electronic health record (EHR) approximately 7 days

after enrollment. Dosing and prescribing recommendations were included in the genotyping report uploaded to the medical record, based on prescribing algorithms published by CPIC or DPWG (Supplemental Table 1). A clinical adjudication committee staffed by a rotation of 7 American Board of Clinical Pharmacology certified or eligible physicians and other study investigators met weekly to review all genotype information in the context of each patient's medication list. The adjudication committee contacted the prescribing clinician through an EHR message to reinforce the genotype-guided prescribing recommendations in case of actionable genotype results. The prescribing clinician was offered a clinical pharmacology consult if questions persisted as part of the study. All care was delivered at the behest of the subjects' standard medical team, and the study team did not place any prescriptions. Keeping with the pragmatic nature of the trial, the providers were not individually asked if they were willing to follow the recommendations.

Subjects randomized to the standard care arm were not genotyped. A waiver of consent was authorized because these subjects received no intervention. The protocol was designed this way as a pragmatic trial, to minimize interference with normal practice for the control group. Outcome data from the year preceding and the year following the index prescription were extracted from the EHR.

Genotyping

A custom polymerase chain reaction (PCR) based OpenArray® (TaqMan™ assay, ThermoFisher, Waltham MA) pharmacogenotyping test including 43 variants in 13 genes was completed from blood or saliva samples upon enrollment of subjects in the intervention arm (Supplemental Table 2). Copy number variations of *CYP2D6* were assessed by TaqMan™ assay that targets exon 9 using 96-well plates. All genotyping was done in a College of American Pathologists (CAP) accredited and CLIA certified laboratory in the Indiana University School of Medicine.

Outcomes

The outcome assessed in this study was the occurrence of ADEs during 1 year follow-up. ADEs were defined according to the National Institute of Health's Common Terminology Criteria for Adverse Events (CTCAE), modified where necessary. All efficacy and ADE outcomes were determined through EHR data extraction. These outcomes were defined using a combination of ICD9/10 diagnoses, laboratory tests, medication records, encounter types (e.g., inpatient), and the participant's sex (Supplemental Table 3). Particular efficacy and ADE outcomes were analyzed for index medications (Supplemental Table 4), based on the literature (Supplemental File 5)¹⁷⁻⁴⁵. Relevant ADEs were assigned to each of the 26 drugs based on frequency and specificity in the literature. The corresponding ICD9/10 codes are provided in Supplemental Table 6. The severity of the ADEs was determined according to modified CTCAE criteria. In some cases, new medications prescribed to treat ADEs were used as evidence of an ADE, such as naloxone for opioid overdose (Supplemental Table 7). Potential drug-drug interactions were queried for 192 medication ingredients in the cohort and were assessed as a covariate in the propensity matched analysis described below (Supplemental Table 7). The analysis periods (windows) selected for the outcomes varied by index medication (Supplemental Table 8). ADEs (or efficacy outcomes) had to occur

within the window for an individual to be counted as having an outcome associated with the index medication. For example, if warfarin was the index medication, a gastrointestinal bleed observed on day 120 would be considered an ADE, but a bleed occurring on day 121 would not.

The ADE outcome described in this study was pre-specified, but the study was not powered for this outcome. The primary outcome for which the INGENIOUS trial was powered was total health care costs. As described in the adaptation section below, recruitment was expanded beyond the safety-net health system to an academic medical center. Because of differences in definitions and measurement, it was not possible to combine the financial data from these two health systems in order to perform the originally planned primary endpoint cost analysis.

Sample Size

The INGENIOUS study was initially powered to assess health care costs between the intervention and control arms in a single center randomized controlled clinical trial¹⁶. The trial was not powered to assess the outcome of ADE occurrence across multiple centers. A post-hoc power analysis for ADEs assumed a type I error set at the 5% level. To detect a 10% reduction in ADE incidence, the sample size of 1306 in each arm afforded 20.5% power. Thus, the results from these analyses should be used to guide future sufficiently powered trials in some populations, rather than definitively testing the impact of pharmacogenetic testing on ADEs.

Randomization

A block randomization scheme was conducted for each medication separately to ensure that medications were assigned to the two arms of the trial equally. A randomization algorithm assigned genotype or no-genotype before patient recruitment. Of the 16,196 randomized to the genotype intervention, only 8.1% (N = 1314) consented to the study. There were 3144 individuals allocated to the no-genotype arm. The randomization algorithm continuously adapted to maintain a 1 to 2 ratio of individuals enrolled in the genotype and no-genotype arms respectively. The overall randomization ratio (intervention:control) varied over time (min: 1:2, max: 9:1) with an average of 5.2 patients randomized to the genotype arm for every patient randomized to the no-genotype arm. Due to the bias introduced by the lower enrollment rate in the genotype arm, the study analysis was adapted from that of a randomized controlled trial to a 1:1 propensity matched cohort model as described below.

Adaptations

Adaptations to the trial protocol and planned analyses were required secondary to a mid-trial change in the EHR of the initial hospital system and a lower-than-expected rate of agreement to enroll in the genotyped arm. The trial began as a single center study in a safety-net health system. Clinical decision support (CDS) alerts were implemented into the EHR to support the trial for real-time recruitment of subjects while in clinic. The CDS recruitment alert fired when an index prescription was placed, which allowed a local research staff member to enroll the subject and obtain a genotyping sample during the clinic visit. During the trial, the safety-net health system transitioned to a new EHR system, which

resulted in a nine month pause in recruitment. The trial was restarted as a multicenter study at the urban safety-net system and a large academic health care system, without a CDS component in the EHR at either center. CDS for return of results was removed, and direct messaging to prescribers by the adjudication committee replaced CDS return of results. Real-time CDS recruitment was replaced by phone calls to patients requesting them to return to provide a genotyping sample within 5 days. A lower-than-expected enrollment rate was observed in the genotype arm. Because the actual enrollment rate was 8.1% instead of the planned 80%, the study analysis was adapted from that of a randomized controlled trial to a propensity-matched cohort study with an expected sample size of at least 1300 in each arm.

Propensity Matching and Statistical Analysis

The R package MatchIt was used to derive a 1-to-1 propensity matched treated-and-untreated cohort. The propensity score matching was based on age, care setting, category of index medication, count of outpatient visits, *CYP2D6* drug-drug interaction status, gender, institution (safety-net or academic system), race, sum of comorbidities (defined by the Johns Hopkins Adjusted Clinical Group Clinical Classifications Software⁴⁶), and year of index medication. Each treated patient was matched with an untreated patient based on the nearest neighbor algorithm.

The genotyped subjects and their propensity score matched cohort were analyzed. The odds ratios (ORs) and their 95% confidence intervals (CIs) for all treatment-outcome pairs were estimated by using the R function Fisher test. Fisher's exact tests were conducted to investigate the relationships between treatment and outcomes. Unadjusted p-values under the Fisher's exact tests were computed. Subgroup analyses by age, institution, and index medications were conducted. In all subgroup analyses, ORs, 95% CIs, and p-values under Fisher's exact test were computed. Additionally, the logistic regression models in sensitivity analyses were fitted. Propensity-matching was not performed separately for sub-group analyses. All analyses were conducted in R 4.1.1.

RESULTS

Participants

A total of 19,340 individuals were randomized to the pharmacogenotyping intervention arm (N = 16,196) or the control arm (N = 3,144). Of the 16,196 individuals in the intervention arm, 1,314 provided consent and completed genotyping. Five subjects were removed from the analysis because their index medication was not included in the trial and three additional subjects were not propensity matched. In the control arm, 73 subjects were excluded and 3071 were available for matching. The 1306 in the genotyped group were 1:1 propensity matched to 1306 individuals in the control arm (Figure 1B). Both groups were well matched with a similar number of healthcare encounters in the preceding year and similar co-morbidity scores (Table 1). The distribution of subjects was evenly split between the academic health system (48.9%) and the safety-net health system (51.1%). The mean age of enrollees was 49.6 ± 15.7 years, and 67.5% of subjects were female. The mean body mass index was higher in the genotyped group, and the proportion of individuals who identify as Hispanic was lower. The most common index medication classes were

anti-depressants (43.6%), opioids (27.2%), and proton-pump inhibitors (PPIs, 15.8%). All other drugs accounted for 13.4% of index medications.

Adverse drug events

Subjects randomized to the intervention arm who received pharmacogenotyping had test results uploaded to the EHR. The proportion of subjects with an actionable genotype was 34.7% overall and varied across index medications. The prescribing clinician was contacted with recommendations for genotype-guided dosing or substitutions by the study team (Supplemental Table 1). Relevant adverse events were assessed over the subsequent year according to modified CTCAE criteria (Supplemental Table 3, 4, 5, 6). The overall ADE rate was 16.1%, and the rate of severe ADEs was 3.2%. No significant difference in ADE occurrence was observed between the genotype and control groups when all propensity-matched patients and all ADEs were included (odds ratio 0.96, 95% CI 0.76–1.18, Table 2). After filtering for ADE severity (CTCAE level 3 or higher), the odds ratio of an ADE in the genotyped group was 0.90 as compared to the control arm (95% CI: 0.58–1.40). The overall 1-year mortality was 1.2%, and the odds ratio of death in the genotyping arm was 0.60 (CI: 0.28–1.21, $p = 0.16$) as compared to the control arm. Evaluating for the composite outcome of death or severe ADE, the odds ratio was 0.82 in the genotyped group (95% CI: 0.56–1.19, $p = 0.30$).

Drug-specific adverse drug events

As a set of exploratory analyses, the occurrence of ADEs was assessed for each index medication class in the study (N treated = 20, Table 3). All analyses were underpowered. Significant reductions in composite grade 1–4 ADEs were not appreciated for any drug class. For tacrolimus, no subjects ($N = 4$) in the genotyping arm had ADEs (including tacrolimus levels outside of therapeutic range), while 5 of 7 had ADEs in the control arm ($p = 0.06$). For most psychiatric drugs (selective serotonin/norepinephrine reuptake inhibitors or aripiprazole), a reduction in severe ADEs (grade 3 or 4, OR 0.38, CI: 0.13–0.97) and in the occurrence of the composite severe ADE and death outcome (OR 0.34, CI: 0.12–0.85, $p = 0.017$) was observed in individuals who received pharmacogenotyping (Table 4). Tricyclic antidepressants were assessed separately given their different side effect profile. Proton-pump inhibitors and opioid index medications accounted for 43% of index medications, but genotyped subjects who received these medications did not have any significant improvement in ADEs, severe ADEs, or death. For clopidogrel, ADEs were infrequent with no significant difference between the genotyping and control arm.

Sub-group analyses

Sub-group analyses were conducted across institutions and age ranges (Supplemental Table 9). No significant reductions in ADEs, severe ADEs, or deaths were observed in individuals younger than 45 years of age or those 46 and older. An opposing direction of effect was observed between pharmacogenotyping and ADEs for individuals age 46 and older (OR 0.85, CI: 0.65–1.12, $p = 0.25$) and younger individuals (OR 1.16, CI: 0.82–1.65, $p = 0.39$). No major difference was observed between the safety-net and academic health systems.

Discussion

The INGENIOUS study was an NIH-IGNITE network study conducted to identify and break down barriers to implementing genomic medicine. It sought to determine whether implementation of a panel of pharmacogenetic predictors for 26 drug-gene pairs would aid practitioners in reducing health care costs and avoiding ADEs. In this study, ADEs and their severity were defined according to modified CTCAE criteria and were coded based on discrete EHR data including laboratory tests, diagnosis codes, and medication records.

The trial was conceived as a single center study in a safety-net health system. During its first year, recruitment was an integrated component of the EHR wherein providers were alerted to their patients' eligibility immediately upon placing a prescription. Patients could be enrolled shortly after the index prescription by local research staff. Additionally, CDS alerts were intended to convey genotype-guided dosing recommendations to providers for any subsequent index medications prescribed.

The safety-net health system's EHR was replaced approximately 1 year into the study, after 251 subjects were genotyped. This change had several downstream consequences. First, CDS alerts could no longer be used for recruitment or for subsequent index medication recommendations, which may have impacted results. After the EHR change, the adjudication committee took on a larger role to manually convey recommendations to provider inboxes. Second, enrollment was depressed due to both a temporary trial shutdown and the decoupling of recruitment from the clinic encounter in which the index drug was prescribed. Instead of real-time alerting in the EHR for eligible subjects, research staff were provided lists of eligible patients the day after index prescriptions were made and had 5 days to call, schedule, and receive a genotyping sample from a subject. The percent of subjects enrolled was lower than expected at 8.1% instead of the planned 80% rate. The randomization algorithm of INGENIOUS adjusted to maintain a 2:1 ratio of enrollment in the control and genotype arms, but the selection bias introduced by the enrollment of only 8% of individuals randomized to the intervention arm required a change from a randomized controlled trial comparison to a 1:1 propensity matched analysis. An analysis of the enrollment populations in the INGENIOUS trial was previously reported⁴⁷.

To compensate for the depressed enrollment, an academic health system was added as a second site, which impacted the primary outcome analysis. Each site provided economic data with different definitions and measures which prevented the assessment of the health care cost primary outcome across the entire study population. The ADE analysis presented in this study was conducted across two distinct health systems, one with a safety-net mission and the other with an academic affiliation. ADE occurrence was identified as a pre-specified outcome, although the study was not powered to address this outcome. In INGENIOUS, we observed an odds ratio for reduction in serious ADEs of 0.91 (95% CI: 0.58–1.4), which aligned with the expected effect size of a 10% relative reduction in serious ADEs after pharmacogenotyping. However, the serious adverse event rate was low at 3.2%, and a much larger sample size would be needed to detect a significant 10% reduction in serious ADEs with 80% power.

The diversity of drug-gene pairs included in the study created challenges to compare subjects with different underlying health conditions, but propensity matching compensated to the extent possible. In INGENIOUS, the three most common index medications were anti-depressants, opioids, and PPIs. Other medication classes had small sample sizes which precluded interpretation of drug class specific ADEs. Despite the sample size, a reduction in serious ADEs was detected for a group of psychiatric medications (aripiprazole and the SSRIs/SNRIs). This medication class held the highest frequency of index medication scripts, had a large effect size, and was often prescribed on a long-term basis. These findings formed part of the basis of an on-going randomized controlled trial, ADOPT-PGx, in patients with depression.

A reduction in ADEs was not observed in individuals prescribed opioids in the intervention arm. In a prior interim analysis of INGENIOUS⁴⁸, significant opioid ADEs and inefficacy were found associated with CYP2D6 activity score. Phenoconversion was critical to identifying the signal. In INGENIOUS, the control group did not undergo genotyping, which prevented comparisons across the impaired metabolizers from each group, perhaps partially explaining the discrepancy. Further, INGENIOUS outcomes were obtained informatically from the EHR. This may have reduced the sensitivity and the specificity of the ADE detection. Retrospective EHR data cannot always determine whether an event was caused by a particular index medication. Opioid inefficacy is challenging to ascertain without manual chart search or prospective pain control and opioid dose tracking. Other index medications with low frequency may be subject to genotype imbalance. Also, index prescriptions are not necessarily always filled, nor are medications always taken as prescribed⁴⁸. These lessons gleaned from INGENIOUS informed the future trial design for the IGNITE network's ADOPT-PGx study^{49, 50}. The ADOPT-PGx study is independently powered for each class of medication. Pain control outcomes are prospectively ascertained, and the control arm is ultimately genotyped to facilitate phenoconverted comparisons of impaired metabolizers.

In INGENIOUS, PPIs were included as index medications to expand the breadth of drug-gene pairs queried and to align with data that formed the basis for the current CPIC guidelines. No significant reduction in ADEs or serious ADEs was seen in the genotype-guided group of individuals receiving PPIs. The INGENIOUS enrollment algorithm screened for the presence of *Helicobacter pylori* infection, erosive esophagitis, or other conditions as enrollment criteria for this class of medication. *Helicobacter pylori* infections are often treated with a 14 day course of twice daily PPI dosing with amoxicillin and clarithromycin⁵¹. According to CPIC guidelines, CYP2C19 poor metabolizers are recommended to receive once daily PPI dosing⁵². However, with the ~12-day delay in genotype reporting (5 days for enrollment and 7 days for EHR upload), providers lacked the opportunity to adjust PPI dosing in a meaningful amount of time. This limitation may have impacted the results for other drugs classes as well.

The PREPARE trial identified a 30% reduction in adverse events with genotype-guided therapy for the investigational group (n=3342) versus the non-guided control group (n=3602)^{53, 54}. Compared to the multi-center PREPARE trial, the INGENIOUS trial enrolled half as many patients. Patients were enrolled upon first prescription of an actionable index study drug. The index drugs were similar in both trials. In INGENIOUS, however,

genotyped patients were compared to a control group allocated via retrospective propensity matching, while the PREPARE trial employed a prospective randomized group allocation. This allowed the PREPARE trial to collect real-time patient-reported events for a period of 12-weeks. INGENIOUS patient ADEs were captured retrospectively from the EHR relying largely on ICD9 and ICD10 codes during the one year after patient enrollment. Thus, an important difference between the two trials is based on comparison and collection of phenotypic adverse event information. The INGENIOUS approach has limitations because patient ADE reports to physicians can be underreported and EHR data can be incomplete, which is potentially reflected by differences in the overall ADE rate between studies: 25.2% in PREPARE compared to 16.1% in INGENIOUS. Moreover, ICD9 and ICD10 codes are imprecise and not expansive enough to capture the full range of potential ADEs. Thus, power estimates and methodology in capturing phenotype data may explain the contradictory outcomes and conclusions between the two trials.

In summary, the INGENIOUS study sought to test whether a panel of pharmacogenetic results would impact ADEs in two types of health care systems. However, the results should be interpreted in the context of the multiple study design limitations and unique challenges incurred during the study. Lessons learned from this early study of genomic medicine implementation include that trials evaluating pharmacogenetic genotyping in response to de novo pharmacogenetic actionable prescriptions are likely to require more effective CDS, faster return of results or preemptive testing, consent prior to randomization, larger sample sizes, and assurance that participants are enrolled from providers' clinics that will follow the pharmacogenetic recommendations. This analysis from INGENIOUS should be used to guide future sufficiently powered trials and is not definitive. The results of INGENIOUS helped to inform future trial design for NHGRI's IGNITE consortium and provide additional support for the clinical utility of genotype-guided dosing of antidepressant agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY

Data is available for the INGENIOUS study in dbGaP with study accession: phs001701.v1.p1.

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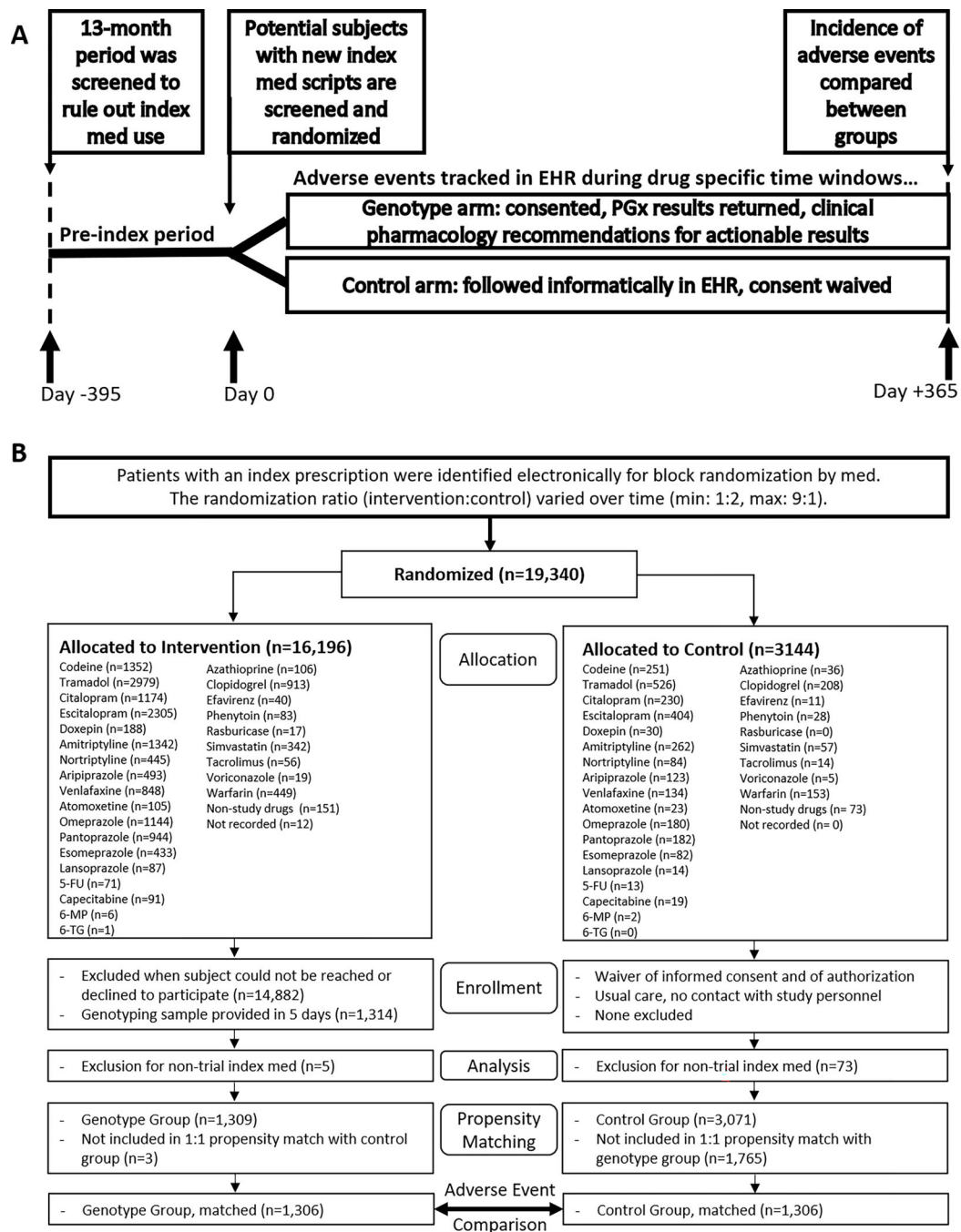
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**Figure 1.**

A) The study timeline. The index medication prescription defined trial day 0. A pre-index period of 13 months preceding day 0 was screened before randomization to ensure that the index prescription was “new”. Subjects in the intervention arm had up to 5 days following the index prescription to consent, enroll, and provide a genotype sample. Genotype results which included recommendations for actionable test results were available within the electronic health record approximately 7 days after sample acquisition. Adverse drug events were tracked for up to 1 year during the follow-up period. The window to track adverse

events was drug specific (see supplemental table 5). Diagnosis codes, medication data, and laboratory test values were queried from the electronic health record in the pre-index period to define pre-existing conditions and were compared to post-index diagnosis codes, medication data, and laboratory test values to define incident adverse drug events. PGx – pharmacogenetic, EHR – electronic health record, med – medication. B) Flow diagram of the clinical trial. The primary comparison was incident adverse drug events between those genotyped and propensity-matched control subjects.

Table 1:

Characteristics of subjects in the genotyped and control arms which were included in the propensity matched analysis.

Characteristic	Genotyped (N=1,306)		Control (N=1,306)		P-value
	Mean or N	SD or Percent	Mean or N	SD or Percent	
Age (Mean, SD)	49.6	14.5	49.6	16.9	0.61
Gender (N, %)					0.96
Female	885	67.8%	878	67.2%	
Male	419	32.1%	426	32.6%	
Unknown	2	0.2%	2	0.2%	
Body mass index¹(Mean, SD)	32.3	9.2	31.0	8.5	0.002
Ethnicity (N, %) ¹					0.002
Hispanic	29	2.2%	62	4.7%	
Non-Hispanic	994	76.1%	975	74.7%	
Unknown	283	21.7%	269	20.6%	
Race (N, %)					0.49
White	799	61.2%	803	61.5%	
Black	452	34.6%	447	34.2%	
Other ²	46	3.5%	40	3.1%	
Unknown	9	0.7%	16	1.2%	
Care setting at enrollment (N, %)					0.90
Outpatient	1088	83.3%	1091	83.5%	
Inpatient	19	1.5%	25	1.9%	
Observation	80	6.1%	75	5.7%	
Emergency Department	38	2.9%	36	2.8%	
Unknown	81	6.2%	79	6.1%	
Year of Enrollment (N, %)					0.76
2015	114	8.7%	99	7.6%	
2016	200	15.3%	200	15.3%	
2017	680	52.1%	690	52.8%	
2018	312	23.9%	317	24.3%	
Institution (N, %)					0.56
Academic center	631	48.3%	647	49.5%	
Safety-net	675	51.7%	659	50.5%	
Index Medication (N, %)					>0.99
Non-TCA antidepressant/ psychiatric ³	380	29.1%	383	29.3%	
Tricyclic Antidepressant ⁴	188	14.4%	189	14.5%	
Opioid ⁵	354	27.1%	356	27.3%	
Clopidogrel	77	5.9%	79	6.1%	

Characteristic	Genotyped (N=1,306)		Control (N=1,306)		P-value
	Mean or N	SD or Percent	Mean or N	SD or Percent	
PPI ⁶	211	16.2%	202	15.5%	
Warfarin	35	2.7%	37	2.8%	
6-MP/Azathioprine	7	0.5%	7	0.5%	
Phenytoin	5	0.4%	7	0.5%	
Voriconazole	1	0.1%	1	0.1%	
Simvastatin	22	1.7%	20	1.5%	
5-Fluorouracil or Capecitabine	19	1.5%	17	1.3%	
Efavirenz	2	0.2%	1	0.1%	
Tacrolimus	4	0.3%	7	0.5%	
Rasburicase	1	0.1%	0	0.0%	
CYP2D6 inhibitor present (N, %) ⁷					>0.99
No	1019	78.0%	1019	78.0%	
Yes	287	22.0%	287	22.0%	
Other clinical variables (Mean, SD)					
Count of outpatient visit	12.3	12.5	12.1	13.5	0.23
Sum of comorbidities ⁸	7.0	3.4	7.0	3.5	0.56

¹Body mass index and ethnicity were not significant covariables in the propensity match.

²Race was included in the propensity match as a trilevel variable including Black, White, and other due to the distribution.

³Non-TCA antidepressant and psychiatric medications include atomoxetine, citalopram, escitalopram, venlafaxine, aripiprazole.

⁴Tricyclic antidepressants include nortriptyline, amitriptyline, doxepin.

⁵Opioids include tramadol and codeine.

⁶Proton pump inhibitors include omeprazole, esomeprazole, pantoprazole, lansoprazole.

⁷Strong and moderate inhibitors were included.

⁸Comorbidities defined by Johns Hopkins Adjusted Clinical Group Clinical Classifications Software group identities.

Table 2:

Primary and secondary outcomes

Group	Genotyped N = 1306 (%)	Control N = 1306 (%)	Odds Ratio (95% CI)	P-value
Any adverse drug event (unadjusted ¹)				
Yes	207 (15.8)	214 (16.4)	0.96 (0.76–1.19)	0.75
No	1099 (84.2)	1092 (83.6)		
Logistic Regression Model (adjusted)			0.96 (0.78–1.18)	0.71
Severe adverse drug event (unadjusted)				
Yes	40 (3.1)	44 (3.4)	0.90 (0.57–1.43)	0.74
No	1266 (96.9)	1262 (96.6)		
Logistic Regression Model (adjusted)			0.91 (0.58–1.40)	0.66
Death (unadjusted)				
Yes	12 (0.9)	20 (1.5)	0.60 (0.26–1.23)	0.21
No	1294 (99.1)	1286 (98.5)		
Logistic Regression Model (adjusted)			0.60 (0.28–1.21)	0.16
Death and/or severe adverse drug event (unadjusted)				
Yes	52 (4.0)	63 (4.8)	0.82 (0.55–1.21)	0.34
No	1254 (96.0)	1243 (95.2)		
Logistic Regression Model (adjusted)			0.82 (0.56–1.19)	0.30

¹Unadjusted determined by Fisher's exact test. Severe adverse drug (ADE) event refers to a grade 3 or 4 ADE according to the modified CTCAE.

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Table 3:

Subgroup analyses of severe adverse events by index medication class

Group	ADE Yes	ADE No	OR (95% CI)	P-value
Clopidogrel				
Genotype	6	71	2.13 (0.44–13.66)	0.32
Control	3	76		
SSRI, SNRI or aripiprazole ¹				
Genotype	7	373	0.38 (0.13–0.97)	0.040
Control	18	365		
Proton-pump inhibitor				
Genotype	14	197	1.12 (0.47–2.74)	0.84
Control	12	190		
Warfarin				
Genotype	1	34	0.34 (0.01–4.45)	0.61
Control	3	34		
Opioid				
Genotype	1	353	1.01 (0.01–79.1)	>0.99
Control	1	355		
Simvastatin				
Genotype	0	22	NA	>0.99
Control	0	20		
Tricyclic antidepressants				
Genotype	11	177	1.61 (0.56–5.03)	0.35
Control	7	182		

¹SSRI - Selective serotonin reuptake inhibitors, SNRI - Selective norepinephrine reuptake inhibitors

Table 4.

Subgroup analysis of death and/or severe adverse drug events by index medication class.

Treated	ADE Yes	ADE No	OR (95% CI)	P-value
Clopidogrel				
Genotype	7	70	1.48 (0.38–6.19)	0.56
Control	5	74		
SSRI, SNRI or aripiprazole ¹				
Genotype	7	373	0.34 (0.12–0.85)	0.017
Control	20	363		
Proton-pump inhibitor				
Genotype	16	195	1.3 (0.56–3.09)	0.56
Control	12	190		
Warfarin				
Genotype	4	31	0.83 (0.15–4.25)	>0.99
Control	5	32		
Opioid				
Genotype	6	348	0.75 (0.21–2.5)	0.79
Control	8	348		
Simvastatin				
Genotype	1	21	0.91 (0.01–74.67)	>0.99
Control	1	19		
Tricyclic antidepressants				
Genotype	11	177	1.4 (0.5–4.13)	0.49
Control	8	181		

¹SSRI - Selective serotonin reuptake inhibitors, SNRI - Selective norepinephrine reuptake inhibitors