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The Feasibility and Potential of Pharmacogenetics to Reduce Adverse Drug Events in Nursing Home Residents

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Keywords

Pharmacogenetics; nursing homes; adverse drug events

Introduction

Many drugs commonly prescribed to nursing home (NH) residents pose potential harms that may outweigh benefits.[1] Some harm may be due to inter-individual drug responses at least partially explained by pharmacogenetics (PGx). PGx is the study of the relationship

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Author's Contributions

CEK, DJC, TW, and CAA were involved in the study concept. CEK and KW were involved in the study design. CEK, KW, MC, AW, SMP, and AHS was involved in the acquisition of subjects and data. CK, JJL, FZ, and DJC were involved in data analysis and/or interpretation of data. All were involved in preparing the manuscript.

Conflicts of Interest

CK became a member of an External Advisory Board to Baptist Health, FL in Precision Health in 2020. Portions of this work were accepted to the annual American Geriatrics Society national meeting in 2020.

between a person's inherited genetics and their responses to different medications.[2] PGx testing in NHs could potentially reduce patient harm and allow prescribers to predict which medications and dosages would be most appropriate before prescribing.[3] A Danish study found that most NH residents were exposed to drugs or drug combinations with PGx-based guidelines.[4] A Canadian study found 90 NH residents had 29 major drug-gene interactions (DGI).[5] We identified no work within U.S. NHs to examine DGI or PGx implications on patient harm. Our aim was to assess the feasibility of pharmacogenetic (PGx) testing among nursing home (NH) residents and evaluate the potential PGx testing benefit in a single NH population.

Methods

We conducted a cross-sectional feasibility study in a single NH as a case series. Residents were ineligible if they were actively dying, discharged, clinically unstable, or had communication barriers such as deafness, blindness, or were not fluent in English. Each resident without a charted dementia diagnosis was approached and screened for memory impairment using the Short Form Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE).[6] Residents with ≤3.30 on the IQCODE were deemed cognitively intact, informed about the study, and invited to participate. For residents with a charted dementia diagnosis or residents who scored ≥3.30 on the IQCODE, their legally authorized representatives (LARs) were contacted for consent and consented. We approached the remaining NH residents, consented those who agreed to participation, and administered the study.

Once consented, a cheek swab was collected using an ORACollect Dx buccal swab collection kit (DNA Genotek, Ottawa, ON, Canada). Samples were processed for DNA extraction, processed, and shipped to OneOme, LLC (Minneapolis, MN, USA) as one batch (n=19) for analysis. The OneOme RightMed® Test multiplex panel determines alleles for single nucleotide polymorphisms (SNPs) in 27 pharmacogenes associated with clinically significant adverse drug events and copy number variation in *CYP2D6*, using TaqMan genotyping and LGC Biosearch BHQ® probe-based methods. The OneOme RightMed® Test also provides reports with expected phenotypic changes due to pharmacogenetic variants, and guidance for drug-gene interactions and has been approved for use by the U.S. Federal Drug Administration with high validity and broad concordance.[7] We defined a "major" DGI as one with known major effects on metabolism and indicative of an elevated risk of adverse reaction or loss of efficacy and a "moderate" DGI as one with moderate effects, per the OneOme Advisor report as provided by Food and Drug Association (FDA), the Clinical Pharmacogenetics Implementation Consortium (CPIC), or other professional associations.

We conducted a targeted chart review to collect resident demographics, current medication list, and other variables. We used descriptive statistics to characterize means with standard deviations or medians with ranges for continuous variables and proportions for dichotomous variables. We calculated the frequency of DGIs by taking the total, major, and moderate DGIs over the total number of medications per participant. Analyses were conducted using

Stata 14.2 (StataCorp LLC, College Station, TX). The study was approved by the University of North Carolina Institutional Review Board (UNC IRB #19-1247).

Results

Among 79 current residents, 12 were discharged or died prior to chart review. Twelve of the 52 residents with dementia had LARs consent to participation. Of the 15 residents without dementia, 7 chose to participate. Seventeen of 19 cheek swabs contained DNA with sufficient quality and quantity for NGS analyses. Most participants were white (90%) and female (62%), and the majority of the 17 NH residents who were successfully genotyped were white (100%) and female (63%).

A total of 150 medications were prescribed to the 17 NH residents with usable PGx data (mean 8.8, standard deviation (S.D.) 3.6; median 10, range 3-14 medications). Thirteen residents (76.5%) had at least one major or moderate DGI (Table 1). Five residents had 11 major interactions (range 1-3 medications per resident). Moderate interactions were discovered for a total of 12 patients on 25 medications (range 1-4 medications). The average total DGI ratio per participant was 0.22 DGIs (Table 2).

Discussion

PGx appears feasible in NHs in that we were able to recruit participants, collect usable samples, perform PGx testing, and identify DGIs. The potential benefits of PGx appear high. Reassuringly, we were able to obtain genetic information from 17 of 19 (89%) samples. This result is similar to a primary care study of older adults >60 years that found 83% of samples resulted in usable genetic material.[8] More than half of NH residents genotyped had major or moderate PGx interactions. The “at-risk” medications included commonly prescribed drugs in older adults, namely, clopidogrel, beta-blockers, antidepressants, and pain medications. While we did not calculate the DGI ratios per medication burden, future work should focus on PGx within the context of polypharmacy. We will also seek to quantify the adverse drug events related to the DGI. CPIC have robust guidelines for all four of these medication classes.[9–11] The potential clinical implications of the PGx testing data appeared subjectively significant. PGx testing may provide a real-world way to attain more precise prescribing, though future work is needed to determine if PGx benefits any specific nursing home populations such as those with co-existing cognitive, renal, or liver impairment. . Pharmacy-led interventions to communicate PGx findings have demonstrated feasibility and changed prescriber behavior.[12,13] However, it remains unclear how to incorporate PGx testing along with other areas of geriatric precision medicine, including multimorbidity and frailty into nursing home care. Further work is needed to fully understand the barriers to PGx implementation in the NH setting and should determine whether major and moderate DGI found via PGx are associated with observable clinical harm.

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Sponsor's Role

The sponsor had no role in the design, methods, subject recruitment, data collections, analysis, or preparation of the manuscript.

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Key Points:

- We identified 11 major drug-gene interactions in 5 of 17 residents.

Why does this matter?

Adverse drug events cause significant harms to older adults and pharmacogenetics may reduce these harms.

Table 1.

Potentially Inappropriate Medications Based on "At-Risk" Drug-Genotype Pairs

Gene Name	At-Risk Drug (n)	Guidance to Clinicians
CYP1A2	**Moderate**: Lidocaine (1) *, Mirtazapine (1)	Lower starting doses may be effective. Monitor for adverse events at standard doses and consider TDM if available.
CYP2C19	**Major**: Clopidogrel (1)	**Major**: Consider initiating another medication (e.g., prasugrel or ticagrelor).
	Moderate: Citalopram (1), Omeprazole (2)	**Moderate**: • For citalopram, initiate a normal dose and monitor closely for slower than expected efficacy. • For omeprazole, initiate the normal dose, but should consider higher starting doses if using for *H. pylori* eradication.
CYP2C9	**Moderate**: Celecoxib (1) Glipizide (2)	• Lower starting doses may be effective. Monitor for adverse events at standard doses and consider TDM if available.
CYP2D6	**Major**: Carvedilol (1), Fluoxetine (1), Hydrocodone (2), Metoprolol (1), Ondansetron (1), Oxycodone (2), Tamsulosin (1), Tramadol (1)	**Major**: • For carvedilol, initiate at normal doses, but monitor closely for dizziness and falls. Do not switch to metoprolol or timolol. • For fluoxetine, lower starting doses may be effective. • For hydrocodone, oxycodone, and tramadol, consider an alternate non-CYP2D6 substrate analgesic; altered metabolism can lead to ineffective analgesia and increased toxicities. • For metoprolol, when patients have increased CNV and ultrarapid metabolism, can consider titrating up to 2.5 times the approved dose. Consider alternative non-CYP2D6 substrate medications (e.g., bisoprolol or atenolol). • For ondansetron, when patients have increased CNV and ultrarapid metabolism, consider alternative non-CYP2D6 substrate medications (e.g., granisetron). • For tamsulosin, when patients are poor metabolizers, do not use the 0.8 mg dose, and use caution with the 0.4 mg dose
	Moderate: Donepezil (1), Hydrocodone (1), Metoprolol (1), Mirtazapine (1), Ondansetron (4), Oxycodone (1), Propranolol (1), Tamsulosin (1), Tramadol (1)	**Moderate**: • For oxycodone and tramadol, initiate a normal dose when intermediate metabolizers, but monitor closely for toxicities. • For other medications, lower starting doses may be effective. Monitor for adverse events at standard doses and consider TDM if available.
CYP3A4/5	**Moderate**: Atorvastatin (1), Diltizazem (1), Hydrocodone (1), Oxybutinin (1), Oxycodone (1)	• Lower starting doses may be effective. Monitor for adverse events at standard doses and consider TDM if available. • For hydrocodone and oxycodone, consider an alternate non-CYP2D6 substrate analgesic; altered metabolism can lead to ineffective analgesia and increased toxicities. If switching to an alternative, do not use hydrocodone, oxycodone, or tramadol.
OPRM1; Asn>Asp (rs1799971 118A>G)	**Moderate**: Tramadol (1)	Initiate tramadol at normal doses. However, altered metabolism could require higher doses for equivalent analgesia, and patients could be at an increased risk for toxicities. If switching to an alternative, do not use hydrocodone, or oxycodone.
SLC6A4	**Moderate**: Citalopram (1)	Initiate a normal dose and monitor closely for slower than expected efficacy.
SLCO1B1	**Moderate**: Atorvastatin (2); Simvastatin (1)	• Clinicians should consider initiating at lower doses, or consider an alternative statin that is not a substrate for this efflux transporter (e.g., rosuvastatin). Consider routine CK surveillance. • For simvastatin, the U.S. FDA recommends against using the 80 mg dose in these patients unless the patient has already tolerated it for ≥ 12 months.

* Denotes guidance only applicable to systemic (non-dermal) dosage forms, and "n" in the At-Risk Drug column indicates the number of participants with the drug-genotype pair.

Abbreviations: CK, creatine kinase; CNV, copy number variation; TDM, therapeutic drug monitoring; U.S. FDA, United States Food and Drug Administration.

Table 2.

Polypharmacy and Drug-Gene Interaction Ratio Per Patient

Patient	Drugs Prescribed (n)	Drugs Prescribed	DGI ratio (Overall)	DGI ratio (Major Only)	DGI ratio (Moderate Only)
1	14	*Atorvastatin*, anastrozole, apixaban, furosemide, glipizide, insulin lispro (Humalog), levothyroxine, liraglutide, lisinopril, metformin, metoprolol, nystatin, pioglitazone, ranitidine	0.07	0	0.07
2	10	*Citalopram*, *glipizide*, *tamsulosin*, carbidopa/levodopa, dulaglutide, enalapril, fish oil (OTC), ketoconazole, oxybutynin, simvastatin	0.30	0	0.30
3	6	*Mirtazapine*, acetaminophen (OTC), albuterol, amlodipine, donepezil, enoxaparin	0.17	0	0.17
4	13	**Fluoxetine**, **hydrocodone**, **tamsulosin,** *donepezil*, *omeprazole*, *ondansetron*, ASA (OTC), folic acid (OTC), lamotrigine, levetiracetam, magnesium (OTC), promethazine, simvastatin	0.46	0.23	0.23
5	3	Alendronate, folic acid (OTC), morphine	0	0	0
6	9	*Atorvastatin*, *diltiazem*, acetaminophen (OTC), dabigatran, docusate (OTC), insulin glargine (Lantus), insulin lispro (Humalog), metformin, sertraline	0.22	0	0.22
7	14	**Carvedilol**, **oxycodone**, *lidocaine*, *omeprazole*, *ondansetron*, acetaminophen (OTC), ASA (OTC), diclofenac, gabapentin, losartan, pravastatin, prednisone, quetiapine, tacrolimus	0.36	0.14	0.21
8	4	*Ondansetron,* adenosine, carbidopa/levodopa, diclofenac,	0.25	0	0.25
9	10	**Oxycodone,** *oxybutynin*, *propranolol*, acetaminophen (OTC), atenolol, escitalopram, hydrocortisone, losartan, omeprazole, primidone	0.30	0.10	0.20
10	11	*Ondansetron*, *oxycodone,* acetaminophen (OTC), amlodipine, atorvastatin, insulin aspart (Novolog), insulin glargine (Lantus), levothyroxine, lidocaine, lisinopril, omeprazole	0.18	0	0.18
11	10	*Celecoxib*, *glipizide*, *hydrocodone*, *metoprolo*l, ASA (OTC), atorvastatin, furosemide, metformin, pregabalin, ramipril	0.40	0	0.40
12	6	*Simvastatin*, *tramadol*, ASA (OTC), donepezil, losartan, sertraline	0.33	0	0.33
13	5	**Hydrocodone**, **tramadol**, ASA (OTC), enoxaparin, simvastatin,	0.40	0.40	0
14	12	**Clopidogrel**, **metoprolol**, **ondansetron**, *lidocaine*, acetaminophen (OTC), ASA (OTC), ciprofloxacin, docusate (OTC), gabapentin, ibuprofen (OTC), lorazepam, morphine	0.33	0.25	0.08
15	10	ASA (OTC), acetaminophen (OTC), furosemide, gabapentin, ibuprofen (OTC), levothyroxine, metoprolol, ondansetron, oxycodone, tizanidine	0	0	0
16	10	acetaminophen (OTC), ASA (OTC), docusate (OTC), glipizide, lisinopril, memantine, metformin, nystatin, pravastatin, ranitidine	0	0	0
17	3	Acetaminophen (OTC), docusate (OTC), famotidine (OTC),	0	0	0
TOTALS	**150**	--	**0.22**	**0.07**	**0.16**

Predicted major drug-gene interactions are bolded, while predicted moderate drug-gene interactions are italicized.

Abbreviations: ASA, aspirin; DGI, drug-gene interaction; OTC, over the counter