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Main author(s):

| | |
|---|---|
| Prof. Maurizio Taglialatela MD PhD | FOUND |
| Prof. Mauro Cataldi, MD Phd | FOUND |

Other author(s):

| | |
|---|---|
| Robert Vander Stichele | I-HD |
| Dipak Kalra | I-HD |
| Alberto Longo | DWIZ |
| Lucia Comnes | DWIZ |
| Alexander Berler | GNOMON |
| Catherine Chronaki | HL7 |


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## 2. Deliverable abstract

Polypharmacy, commonly occurring in older adults, is an important risk factor for drug toxicity. Medicine review, i.e., the analysis of drug prescriptions with the aim to replace or deprescribe inappropriate or potentially dangerous drugs, is an important tool to reduce drug toxicity. This process is time-consuming and may benefit from the adoption of specific *clinical decision support systems* (CDSS). Even when supported by CDSS, medicine review is slowed by the need to extrapolate the names of the active principles from the brand names of the prescribed drugs. Therefore, it could benefit by the use of *Identification of Medicinal Products* (IDMP) codes to identify medicinal products rapidly and univocally. Randomized clinical trials showed that medicine review reduces inappropriate drug use, but has a minimal impact on hard clinical endpoints, possibly because these only improve in high-risk patients. By enhancing patient sensitivity to drug-drug interactions, variants in genes controlling important steps in drug responses (from pharmacokinetics/PK to pharmacodynamics/PD) may play a critical contribution in defining whether a patient is at high risk for drug toxicity. Specifically, reduced-function variants may enhance the sensitivity to inhibitors of the respective PK-related gene products, whereas high function variants may increase their susceptibility to the potentiating effects of their inducers. Based on these considerations, medicine review could benefit from pharmacogenomic-guided patient selection. With the aim of obtaining information useful to achieve this goal, we examined drug utilization in a cohort of older adults on polypharmacy at the Federico II University Hospital, and we identified the polymorphic pharmacogenes which could be responsible for drug-gene interactions in these patients and the drugs that could more likely be involved in such interactions. The results of this study are instrumental for the planned clinical pilot to identify drug-drug-gene interactions in the real-world setting of a geriatric outpatient clinic, which will be the object of the next-due deliverable D.10. The final goal of these investigation will be to collect the clinical information needed for the future design of pharmacogenomic- and IDMP-based CDSS for medicine review, also considering that, in accordance with our literature and web searches, very few pharmacogenomic-based CDSS are yet available, and none uses IDMP coding for product identification.

Keywords:

Adverse drug reactions, drug-drug interactions, drug-gene interactions, drug-drug-gene interactions, clinical decision support systems, older adults, pharmacogenomics, precision medicine

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# 3. List of abbreviations

| Abbreviation | Complete form |
|---|---|
| ABC1B1 | ATP binding cassette 1B1 |
| ACB | Anticholinergic Burden |
| ADR | Adverse Drug Reactions |
| AI | Artificial intelligence |
| AIFA | Agenzia Italiana del Farmaco |
| ALDH2 | Aldehyde Dehydrogenase 2 |
| AMOVA | Analysis of Molecular Variance |
| AOX1 | Aldehyde Oxidase 1 |
| ATC | Anatomical Therapeutic Chemical |
| BAAT | Bile Acid Coenzyme A Aminoacid N-AcylTransferase |
| BPSD | Behavioral and psycological symptoms of dementia |
| IBenC | Benchmarking Costs and outcomes of community care |
| ICD | International Classification of Diseases |
| CAD | Coronary Artery Disease |
| CDSS | Clinical Decision Support System |
| CNV | Copy Number Variant |
| COPD | Chronic Obstructive Pulmonary Disease |
| CPOE | Computerized Provider Order Entry |
| CPIC | Clinical Pharmacogenetics Implementation Consortium |
| CYP | Cytochrome P 450 |

| | |
|---|---|
| DDI | drug-drug interaction |
| DGI | drug-gene interaction |
| DDGI | drug-drug-gene interaction |
| DDSIs | drug-disease interactions |
| DPWG | Dutch Pharmacogenetics Working Group |
| EHR | Electronic Health Record |
| EMR | Electronic Medical Record |
| EM | extensive metabolizer |
| FOLH1 | Folate Hydrolase 1 |
| FOUND | Azienda Ospedaliera Universitaria Federico II |
| IDE | Insulin-Degrading Enzyme |
| IDMP | Identification of Medicinal Products |
| IM | Intermediate metabolizer |
| indel | Insertion-deletion |
| NM | Normal metabolizer |
| OATP1B1 | organic anion transporting polypeptide 1B1 |
| ONTOP | Optimal evidence-based Non-drug Therapies in Older People |
| OsMed | Osservatorio sull'impiego dei medicinali |
| PGX | Pharmacogenomics |
| PD | Pharmacodynamics |
| PK | Pharmacokinetics |
| PM | Poor metabolizer |

| | |
|---|---|
| PMS | pharmacy management systems |
| PPI | proton pump inhibitor |
| QoL | Quality of Life |
| SENATOR | Software ENgine for the Assessment and optimisation of drug and non-drug Therapy in Older peRsons |
| SHARE | Survey of Health, Ageing, and Retirement in Europe |
| SIMPATHY | Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly |
| SLC | Solute Carrier |
| SNV | Single Nucleotide Variant |
| SNRI | Serotonin and Noradrenaline Reuptake Inhibitors |
| SSRI | Selective Serotonin Reuptake Inhibitors |
| STOPPFrail | Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy) |
| STRIP | Systematic Tool to Reduce Inappropriate Prescribing |
| UPGx | Ubiquitous Pharmacogenomics |
| YLD | Years Lived with Disability |
| VIP | Very Important Pharmacogene |
| WHO | World Health Organization |

# 1 Executive summary

## Background

Polypharmacy, commonly occurring in older adults, is an important risk factor for drug toxicity. *Medicine review*, the analysis of drug prescription to replace or discontinue inappropriate or potentially dangerous drugs, is an important tool to reduce drug toxicity. This process may be highly time-demanding and may be facilitated by *clinical decision support systems* (CDSS), which, however, still need the preliminary identification of the active principles contained in a medicine starting from its brand name. This initial step of medicine review could greatly benefit from the adoption of *Identification of Medicinal Products* (IDMP) codes, which could automate and speed-up the unequivocal identification of the medicines taken by the patient. Randomized clinical trials showed that medicine review decreases the number of prescribed drugs and of inappropriate prescriptions but has a minimal impact on hard clinical endpoints such as mortality or rehospitalizations. This apparent lack of efficacy could be due to poor selection of those high-risk patients who could really benefit from this intervention. One of the critical factors that could confer a high risk of drug toxicity to specific patients is their genotype and, more specifically, genetic variations in important pharmacogenes encoding key proteins for drug *pharmacokinetics* (PK), which may enhance patient sensitivity to *drug-drug interactions* (DDIs). Specifically, reduced-function variants may enhance the sensitivity to inhibitors of the respective PK-related gene products, whereas high function variants may increase their susceptibility to the potentiating effects of their inducers. As a consequence of these *drug-gene interactions* (DGIs), patients with specific genotypes will be at higher risk of developing serious DDIs when further drugs are added to their therapy. Therefore, the analysis of patient genetic profile with special reference to critical pharmacogenes, could help in the selection of patients that mostly need and, more importantly, may benefit from, medicine review.

## Aim of the study

The present study aimed to:

1. Identify potential DGIs (also including those affecting the susceptibility to develop serious DDIs) in older adults from Southern Italy;
2. Examine whether genomic-based CDSS, which may identify potential DGIs and suggest therapy adjustment depending on patient genotype, are already available for use in clinics and whether there could be any interest in designing/implementing new genomic-based CDSS using IDMP coding.

## Methods

To identify DGIs that could affect the susceptibility to DDIs in older adults from Southern Italy, we first identified the polymorphic genes that are more likely to be involved in the PK of drugs taken by these patients and, then, we looked at drugs that could potentially enhance the effect of the genetic variants of these pharmacogenes. We considered as relevant those pharmacogenes which encoded enzymes, pumps or transporters involved in the PK of drugs prescribed to more than 5% of older adults who underwent medicine review at the Clinical Pharmacology Division of the *Azienda Ospedaliera Universitaria Federico II* in Naples, ITALY (FOUND) during the last three years. Data on the prevalence of the most frequent allelic variants of each of these pharmacogenes in Europe, in Italy and, when available, in Southern Italy were retrieved from major

*pharmacogenomic* (PGx) databases. Then, to identify potential DGIs in our cohort of patients, we cross matched the list of the drugs prescribed to older adults at FOUND with those of the inhibitors and inducers of the enzymes, pumps and transporters encoded by the relevant pharmacogenes. By this means, it would be possible to detect patients with poorly functional gene variants who should be more susceptible to inhibitors of their gene products, and patients bearing hyperfunctional variants who should be more susceptible to inducers. The final result of this analysis was a list of potential DGIs that could occur in older adults from Southern Italy, which could lead to the detection of DDGIs in the pilot study being currently planned in the context of the deliverable D8.10.

To identify those CDSS, either already available or under development, which incorporate information on genetic variants in their therapy evaluation, and to investigate whether any of them was designed for future IDMP implementation, we searched the web and the current scientific literature using CDSS, pharmacogenomics, gene variants, drug-gene interaction and IDMP as keywords.

## Results

*Drug utilization in older adults at FOUND*

We examined drug prescription in 369 older adults (median age [IQR]: 74,0 years [69,0-79,0]; 159 females) who underwent medicine review at FOUND. Thirty-three drugs had been prescribed to more than 5% of the patients of our cohort. Most of them were cardiovascular drugs; *proton pump inhibitors* (PPIs) for gastroprotection during antiplatelet therapy; and antidiabetic drugs; the list also included allopurinol, a drug for hyperuricemia, tiotropium an anticholinergic drug for *chronic obstructive pulmonary disease* (COPD), rifaximin, an antibiotic frequently prescribed for colonic diverticula, and tamsulosin, an alpha-adrenergic blocker for prostate hyperplasia.

We identified CYP3A4/5, CYP2C9, CYP2C19 and CYP2D6 as the enzymes encoded by polymorphic genes that metabolized most of the drugs in our list of frequently prescribed drugs (33.3% drugs for CYP3A4/5, 18.2% for CYP2C9, 21.2% for CYP2C19 and 15.2% for CYP2D6) and OATP1B1 (SLCO1B1) and PgP/MDR1 (ABCB1) as polymorphic transporter and pump carrying the majority of them (9.1% for OATP1B1 and 36.4% for ABCB1). In further analysis on allele frequencies and DGIs we focused on the mentioned CYPs and on SLCO1B1 whereas we did not consider ABC1B1 further, since the role of its genetic variation in drug PK is still controversial and probably small.

*Prevalence of polymorphic variants of major pharmacogenes in Southern Italy and potential DGIs that they might cause*

Database and literature search showed that more than 5% of the Italian population bear at least one low-functioning allele of CYP3A4. In Southern Italy, a prevalence of 6% of the *1/*22 diplotype has been reported. These intermediate metabolizer (IM) subjects are expected to be more susceptible to CYP3A4 inhibitors and, based on the prescription data of our cohort, the possible culprits of DGIs involving this cytochrome in older adults could be the antiarrhythmic drug amiodarone, the calcium channel blockers diltiazem and verapamil and the two PPIs, omeprazole and pantoprazole. About 10% of the Italian population has one copy of the normal CYP3A5*1 allele and the only study available in people from Southern Italy reported a prevalence of 13% for the *1/*3 and of 1% for the 1*/1* diplotype. The effect of CYP3A4/5 inducers may be potentiated in

patients with at least one *1 allele but none of these molecules is in the list of the drugs usually prescribed to older adults at FOUND.

Available evidence suggests that about 20% of the Italian population may have a lower-than-normal CYP2C9 activity with no major differences among different regions. People with these low-function variants could be more sensible to drug inhibitors of this CYP than normal. Looking at the list of the drugs commonly prescribed to older adults at FOUND we identified amiodarone, fenofibrate, paroxetine, sertraline as the most likely DGIs in the elderly in Southern Italy.

About 12.7% of the population from Southern Italy carries the CYP2C19 IM *1/*2 diplotype and is expected to be highly susceptible to DGIs involving inhibitors of this cytochrome, some of which, namely the PPIs esomeprazole, lansoprazole and pantoprazole and the *Selective Serotonin Reuptake Inhibitors* (SSRIs) citalopram, fluoxetine and fluvoxamine, are drugs frequently prescribed to older adults at FOUND.

In people from Southern Italy, the prevalence of CYP2D6 PM is virtually zero, whereas about 10% of the individuals have IM diplotypes (*4/*41 and *41/*41) and 3.6% UM diplotypes (*1/2xN). CYP2D6 drug inhibitors that are often used in older adults at FOUND and which could be involved in DGIs with IM variants of this cytochromes are the strong CYP2D6 inhibitors fluoxetine, paroxetine, fluvoxamine, metoprolol, and the weak inhibitors amiodarone, amlodipine, citalopram, escitalopram, lansoprazole, omeprazole, ranolazine, sertraline, verapamil.

A poorly functioning SLCO1B1 phenotype occurs in about 4% of the Italian population whereas more than 35% of the subjects have an intermediate function phenotype. The only study specifically investigating the prevalence of SLCO1B1 variants in the Campania region of Southern Italy reported an unexpectedly high prevalence (82.9%) of homozygous for the poorly functioning variant rs4149056 of SLCO1B1 but these data need to be further confirmed. Among the drugs commonly prescribed to older adults at FOUND, several could potentiate the effect of these gene variation by further blocking an already less than normally functioning SLCO1B1 carrier; these include atorvastatin, digoxin, levothyroxine, pantoprazole, rosuvastatin, valsartan and verapamil.

*Pharmacogenomic-based CDSS*

Several PGx-based CDSSs have been developed already. Most of them are prototypes or closed system developed at universities for the internal use at their University Hospital upon integration with local *Electronic Health Record* (EHR) systems. These local systems are usually only centered on drugs needing dose adjustments or replacement in patients bearing specific gene variants and, in most cases, do not incorporate tools for DDI or DDGI analysis. Only few PGx-based systems have been commercially developed for large-scale use. In these commercial systems, PGx data interpretation is part of a more complex clinical analysis which also incorporates DDI and DDGI evaluation; such systems may also provide integration with EHRs, *Electronic Medical Record* (EMRs), *Computerized Provider Order Entry* (CPOE), and *Pharmacy Management Systems* (PMS) .

None of the PGx-based CDSS that we examined has been specifically designed for older adults and/or uses IDMP codes for rapid and effective drug identification at the time of medicine review.

## Conclusions and future perspectives

The results of our study showed that, in Southern Italy, the prevalence of allelic variants affecting the activity or expression of major pharmacogenes ranges from 5 to 35% depending on the pharmacogene considered. Unfortunately, we did not find any data on the prevalence of concurrent variants in multiple pharmacogenes and, therefore, we cannot predict how often more than one pharmacogene is mutated in a single patient. The analysis of drug prescriptions in older adults on polypharmacy, who are followed at FOUND, suggested that pharmacogene variants may establish relevant DGIs with drugs commonly taken by geriatric patients, thereby enhancing the risk of drug toxicity or reduced drug activity. Therefore, selected genetic factors should be taken into account in medicine review and possibly incorporated in the CDSS used to support this process. Our search showed that very few genomic-based CDSS have been developed so far and that none of them is specifically designed for geriatrics or for the future implementation of IDMP-coding, which could allow a faster and more effective drug identification. In conclusion, our study provides strong arguments to suggest that new IDMP- and genomic-based CDSS should be developed to support medicine review in geriatrics. The list of potential DGIs that we obtained will be instrumental for the future pilot to identify drug-drug interactions that could be potentiated by DGIs in older adults, which we will perform as part of the planned activities of UNICOM WP8.

# 2. Introduction

## 2.1 Drug Toxicity: still an urgent public health problem in the EU

Drug toxicity is still highly prevalent worldwide and implementing corrective measures to reduce its occurrence is, therefore, a top priority in public health. According to the European Commission, in 2008 about 5% of all hospital admissions were due to drug toxicity and *adverse drug reactions* (ADR) were the 5th cause of in-hospital death (European Commission, 2008). A review of the epidemiological studies on drug toxicity prevalence in Europe published from 2000 to 2014 estimated that it was responsible for 3.5% of all hospital admissions and, worryingly, that about 10% of all hospitalized patients developed at least one ADR during hospital stay (Bouvy et al., 2015). In the same review it was estimated that about 0.5% of all ADR are lethal. Similar figures have been obtained in other countries; for instance, Lazarou et al. (1998) showed that in the United States ADRs occurred in 10.9% of the hospitalized patients and that drug toxicity was the cause of 4.7% of all hospital admissions, representing the fourth leading cause of death. The Global Burden of Diseases, Injuries, and Risk Factors Study 2017 (GBD 2017) investigators reported that 34 975 000 adverse effects of medical treatment occurred in 2017 globally, and that they caused 356 500 years lived with disability (YLD); drug toxicity accounted, therefore, for about 1/1000 of all causes of YLD (GBD, 2018). Despite the increasing awareness of the clinical relevance of drug toxicity, its prevalence has been growing during the last years as shown, for instance, by the data of the English MiDatabank for the time interval between 2011-2016 (MiDatabank Adverse Drug Reaction (ADR) reporting). Moreover, the GBD study reported an increase of drug toxicity prevalence by 18.5% from 1990 to 2007 and by 19.6% from 2007 to 2017. In 2017, drug toxicity ranked 25th among all causes of death worldwide, 9th in the United States and 14th in Western Europe (16th in Italy and in France, 15th in Germany and Belgium, 14th in Spain).

Through the analysis of the safety reports uploaded between 1 January 2010 and 31 December 2019 in *Vigibase*, the *World Health Organization* (WHO) global database of individual case safety reports, Montastruc et al. (2021) estimated that 1.34% of ADR are fatal. Based on these alarming data, in 2017 WHO identified the reduction of severe, avoidable harm related to medications by 50% over 5 years, globally, as the goal of the third Global Patient Safety Challenge on Medication Safety (WHO, 2017).

## 2.2 Factors increasing the risk of Drug Toxicity: the special case of older adults on polypharmacy

Several factors may favor the occurrence of drug toxicity, including inappropriate prescription (i.e., giving the drug in the absence of an approved indication or in the presence of a definite contraindication), inadvertently taking a wrong drug instead of the one that was prescribed (because, for instance of similar brand names, similar boxes or similar size or color of the pills), or taking a toxic amount of the right drug (often because of suicide attempts). In addition, when the *right drug* is taken in combination with certain other drugs, *drug-drug interactions* (DDI) may occur, leading to an enhancement or a decrease of drug's effects, and the development of drug toxicity or therapeutic failure, respectively (Anastasio et al., 1997; Carpenter et al., 2019; Merel and Paauw, 2017; Tannenbaum and Sheehan, 2014). Certain disease states such as renal or liver failure may

impair the elimination of specific drugs, therefore causing their accumulation in the blood and the appearance of toxicity. In addition, certain drugs prescribed to treat a specific disease may worsen other diseases of which the patient suffers, causing the so-called *drug-disease interactions* (DDSIs), as it happens, for instance, when drugs with anticholinergic properties such as many psychotropic drugs and antihistamines worsen cognition in patient with dementia or when β-blockers taken for heart failure induce bronchoconstriction in patients with COPD or asthma (Hanlon et al, 2017).

In specific groups of patients, such as those with chronic diseases like diabetes, ischemic cardiopathy or chronic kidney disease, many of the previously mentioned factors may occur in combination. Many patients suffer from several chronic diseases which may occur as comorbidities of their main disease status. For instance, very often patients with *coronary artery disease* (CAD) are also diabetic (as they developed CAD as a complication of long-standing diabetes) and have chronic renal failure (because of the damage caused by diabetes on kidneys). In these multimorbid patients, multiple drugs must be given in combination to treat the different coexistent diseases. In addition, many chronic diseases (e.g., arterial hypertension or diabetes) respond poorly to monotherapy and need the administration of multiple drugs to be effectively controlled. As a consequence of the high number of drugs taken, chronic patients will be at high risk of DDIs. In addition, these patients also frequently have either chronic renal or liver failure, which impair drug metabolism and/or elimination and enhance drug toxicity and they are at risk of DDSI because of their multiple comorbidities. The direct correlation existing between the number of drugs taken, DDIs and drug toxicity has been well established (Johnell and Klarin, 2007), with a conventional threshold set at 5 drugs with systemic effect, concomitantly and chronically taken, to define a multiple drug therapy as risky. This condition is known as polypharmacy; although other definitions of polypharmacy have also been proposed, this is the most widely accepted (Masnoon et al., 2017).

Older adults represent a special group of polypharmacy patients. They show indeed all the aforementioned characteristics of chronic patients plus additional age-related risk factors for drug toxicity including, for instance, age-related changes in PK, difficulties in remember which drug they took and in which amount, difficulties in identifying the pills they take (Cataldi et al., 2017). Since they very often suffer from multiple comorbidities, older adults are usually on polypharmacy. Whereas often polypharmacy may be necessary to adequately treat patients with multiple comorbidities, sometimes it includes unnecessary or inappropriate drugs and is defined as “excessive”. The prevalence of polypharmacy in older adults varies between 10 and 90% depending on gender (being usually higher in females, also because they usually live longer than males and are, therefore, more represented among older adults), age (increasing with age till 85 years to flatten thereafter) and the region where they live (Khezrian et al., 2020). The *Survey of Health, Ageing, and Retirement in Europe* (SHARE) showed that the prevalence of polypharmacy among older adults in retirement homes ranges from 26.3 to 39.9% with the lowest values in Switzerland, Croatia and Slovenia and the highest in Portugal, Israel and the Czech Republic; Italy was in between with an average prevalence of 32.5-34.9% (Midão et al., 2018). The Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly’ (SIMPATHY) project estimated a prevalence of excessive polypharmacy (i.e taking 10 or more drugs) of about 20% among older adults aged 70–74 (Mair et al., 2017). The Benchmarking Costs and

outcomes of community care (IBenC) study showed that the prevalence of polypharmacy among older adults in Home Care in Europe is 39.0% and that 23.1% of them is on excessive polypharmacy (Giovannini et al, 2018). Data from the *Osservatorio sull'impiego dei medicinali (OsMed)* of the Italian Drug Agency (*Agenzia Italiana del Farmaco, AIFA)* showed that the average number of drugs taken by adults aged less than 65 years is 1.9 and it progressively increases with age up to 7.4 in the age group between 80 and 84; thereafter it starts decreasing averaging 2.8 among individuals older than 95 years (Onder et al, 2016; Onder et al, 2014). As expected, DDIs and DDSI occur very frequently in older adults. For instance, Hanlon et al. (2017) showed that more than 25% of the 3055 adults aged 70-79 participating to the Health Aging and Body Composition Study showed at least a potential DDI and more than 16% of them a potential DDSI.

Because of all the above-mentioned factors, drug toxicity is common in older adults. A systematic review of the literature showed that about 10% of them experience an ADR requiring hospitalization and that 11.5% of them undergo an ADR during hospital stay when hospitalized for other reasons (Alhawassi et al., 2014). Not only, ADRs are worrying in older adults because they may lead to serious toxicity needing hospitalization, but they also have a very negative impact on the *quality of life* (QoL) of these subjects for several reasons; for instance, due to their pharmacodynamics properties, anticholinergic drugs may impair cognition and increase the risk of falls, antiadrenergic drugs and vasodilators may cause orthostatic hypotension, dizziness and syncope and benzodiazepines may cause sleepiness and worsen cognition as well (Peron et al., 2011). Therefore, specific interventions have been implemented over the years for the prevention and the early identification of drug toxicity in the elderly.

## 2.3 Tools to decrease the risk of drug toxicity in clinical practice: Medicine Review and supporting clinical decision support systems (CDSS)

Most of the ADR observed in clinics, especially among older people, are (theoretically) preventable by using specific interventions aiming to optimize drug therapy; the majority of ADR are, indeed, due to wrong prescription or lack of monitoring whereas errors in transcription, dispensing, and administration are less commonly involved (Gurwitz et al., 2000). Among the tools available for drug therapy optimization, medicine review has a very special role (Blenkinsopp et al., 2012). Medicine review is an umbrella term to design interventions aiming to: 1- identify and substitute or deprescribe inappropriate or potentially interacting drugs in patients on polypharmacy, 2- allow the early identification of drug toxicity and timely modification of the therapy involved, 3-increase patient's adherence to therapy also through shared decision on how the therapy could be improved. According to the NHS *Taskforce on Medicines Partnership and the National Collaborative Medicines Management Services*, medicine review is 'A structured critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimizing the impact of medicines, minimizing the number of medication-related problems and reducing waste' (Shaw et al., 2002). The English Medicines Partnership, 2008 proposed a widely used classification of the different medication use review interventions that distinguish among 1. Prescription Review, 2. Compliance and concordance review and 3. Clinical Medication review. Prescription review is usually performed by a pharmacist without patient present and consists in the analysis of practical issues concerning drug prescription such as cost-

effectiveness. Compliance and concordance review may be performed either by a physician or by a pharmacist or a nurse, and requires patient presence since it consists in interacting with him/her to assess drug adherence and tolerability. Clinical medication review is performed by physicians (usually a team of specialists) with patient presence, and consists in evaluating drug appropriateness, tolerability and adherence, based not only on the discussion with the patient but also on the assessment of clinical and laboratory data (Clyne et al., 2012). According to the Academy of Managed Care Pharmacy, medication review may be: 1- *Prospective*, when it evaluates patient's drug therapy before medication is dispensed, 2- *Concurrent* , when it is an ongoing monitoring of drug therapy during treatment or 3- *Retrospective,* when it is performed after the patient has received the therapy (AMCP, 2019).

One of the main aims of medication review is to evaluate the therapeutic appropriateness of the pharmacological treatment of specific patients. Therapeutic appropriateness can be defined as "*drug prescribing and dispensing based on rational drug therapy that is consistent with criteria and standards*" (AMENDMENTS TO PRESCRIBING, PREPARATION, AND DISPENSING OF PRESCRIPTION DRUGS 2004 GENERAL SESSION STATE OF UTAH, https://le.utah.gov/~2004/bills/sbillenr/SB0114.pdf). WHO stated that "Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and the lowest cost to them and their community." (World Health Organization. Rational use of Medicines. https://www.who.int/activities/promoting-rational-use-of-medicines/). Appropriateness depends not only on the disease status (as usually evaluated by the compliance with international disease-specific guidelines), but also on the general conditions, the age and gender of the patient who has to be treated; specifically, many drugs that could be appropriate for younger adults are inappropriate in older people. Specific consensus papers can be used to evaluate the appropriateness of specific drugs in older people. Among them the most influential are the Beers criteria (American Geriatrics Society Beers Criteria®Update Expert Panel, 2019), the STOPP/START criteria (O'Mahony et al., 2015), the EU(7)-PIM list (Renom-Guiteras et al., 2015) and the German PRISCUS list (Holt et al., 2010). By using these tools, it has been observed that 22.6% of drug therapies in community-dwelling older people across Europe are potentially inappropriate (Tommelein et al., 2015). Another major objective of medicine review is to identify DDIs and DDSIs, to evaluate their potential severity and to suggest the deprescription or the replacement of dangerously interacting drugs. Not only medicine review aims to identify dangerous drugs, but it should also pick out useless drugs that are ineffective for the patient diseases either because they have been wrongly prescribed or because they have been prescribed for previous disease status (e.g., infections) that resolved in the meantime. Removing ineffective or useless drugs is a priority for medicine review since deprescribing could help patients not only to decrease therapy-related risks but also to increase adherence by reducing the so-called pill burden (Cataldi et al., 2017).

The process of medicine review, and especially of clinical medicine review, may be highly time demanding. *Clinical decision support* (CDSS) can be used to speed-up this process also improving its reliability. CDSS can be defined as systems that present structured medical information via technology tools to pharmacists, nurses, or medical doctors to assist them in clinical decisions (Wake et al., 2021). CDSS can be classified as *active* or *passive*, depending on whether they suggest specific actions to be taken by the health stakeholders or just

give information to them to support their totally independent clinical decisions. At a very basic level, CDSS may just focus on DDIs by providing alerts when potentially dangerous drugs are combined. Some of them are available at no charge and are very popular in everyday medical practice such as the drugs.com (https://www.drugs.com/drug_interactions.html) or the Medscape (https://reference.medscape.com/drug-interactionchecker) interaction checkers. At a higher complexity level, some CDSS also examine the appropriateness of drug prescription based on patients' clinical conditions and age. This is, for instance, the case of the *Intercheck* web interface, a web platform in Italian which is freely available upon registration (https://intercheckweb.marionegri.it/) and is largely used for medicine review in Italy. *Intercheck* makes recommendations based not only on DDIs but also on the Beers Criteria (American Geriatrics Society Beers Criteria® Update Expert Panel 2019) and the START/STOPP criteria (O'Mahony et al., 2015) and includes an Anticholinergic Burden (ACB) score calculator and the Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy (STOPPFrail) (Lavan et al., 2017). In addition, this CDSS provides practical recommendation for patients with renal failure and provides drug-related risk calculation in older adults with the GerontoNet ADR Risk Score algorithm (Petrovic et al., 2017). STRIP Assistant (STRIPA) and SENATOR are two CDSS that have been developed for research purposes and have been used in important randomized clinical studies that we will examine in the next section. *STRIPA (STRIP assistant)* (Meulendijk et al., 2015) is a standalone web-based CDSS based on the *systematic tool to reduce inappropriate prescribing* (STRIP), a method to optimize drug prescription which combines the START/STOPP criteria with patient-centered questionnaires on medical history, previous drug therapy and ADRs (Drenth-van Maanen et al., 2018). Also the *SENATOR (Software ENgine for the Assessment and optimisation of drug and non-drug Therapy in Older peRsons)* CDSS uses the START/STOPP criteria to assess drug appropriateness (Lavan et al., 2019). This software, which was designed as part of the activities of a project funded by the European Union's 7th Framework Programme, not only evaluates drug appropriateness but also analyzes DDIs and DDSIs by using both local databases and the Safescript® software, a comprehensive set of national drug databases which combines the Summary of Product Characteristics of ATC coded medications with International Classification of Diseases 10 (ICD-10) coded conditions. SENATOR also provides recommendations about non-pharmacological treatments based using the ONTOP (*Optimal evidence-based Non-drug Therapies in Older People*) tool. OptiMEDs is a web-based tool for multidisciplinary medicine review in older adults which was developed by a consortium between Ghent University, University of Antwerp and RAMIT (a spin-off of Ghent University, www.ramit.be) and is accessible trough a secured web-link (Wauters et al., 2021). The system may retrieve the drug list of specific patients from their EHR and collects information of the drug side effects experienced by the patient, which are entered by nurses through dedicated pharmatools. Using these data, OptiMEDs generates a list of potentially inappropriate drugs based on EU(7)-PIM, START/STOPP-2 and the Beers' list; it also provides information on the anticholinergic burden of therapy by using the MARANTE scoring system. The final result of the OptiMEDs is a list of drugs that could be described also considering life expectancy of the patient.

Several CDSS have been commercially developed and are available on the market for large scale use in clinics. Most of these commercial solutions are fully integrated with EHRs and with CPOE. Artificial intelligence (AI) might improve the performance of CDSS since it allows the systems to learn directly on the

field from medical doctor practical experience; therefore, commercial systems using AI are being developed and some of them are already on the market. Table 1 summarizes some of the most popular CDSS available for use in clinical practice also including AI-based solutions.

A factor that may seriously limit the speed of medicine review and may also complicate designing CDSS, especially if they are intended to be used internationally and not in single countries, is that active principle, which are usually, though not always, the molecules responsible for toxicities or interactions, have to be extracted from brand names of the drugs for further analysis and processing. Adopting univocal codes for drug identification -the main objective of the UNICOM project could greatly help achieving this goal in a rapid and efficient way and therefore the medicine review process could greatly benefit from developing new IDMP-based CDSS.

**Table 1** Examples of commercial CDSS

| Product name | website | Main features |
|---|---|---|
| Cerner Millennium | https://www.cerner.com/se/en/solutions/millennium | An EHR, with a decision support with duplicate order checks, integrated drug database, rules engines, and an embedded executable evidence-based content. |
| PINC AI™-Stanson Health-A premier company | https://stansonhealth.com/clinical-decision-support/closed-loop-cds-platform | An AI assisted platform, fully integrated with the workflow of patient EMR to mine patient record and provide in real-time evidence-based care, while reducing unnecessary costs; it includes one of the largest proprietary DDI database. |
| Dragon Medical OneNuance | https://www.nuance.com/healthcare/artificial-intelligence.html | AI powered CDSS with voice recognition interfaced with Wolters Kluwer Health *Up to Date*. |
| IBM Micromedex with Watson (Truven/IBM) | https://www.ibm.com/products/micromedex-with-watson | AI and evidence-based system supporting clinical decision, which includes information on DDIs, dosages, IV compatibilities, and a medical literature search engine. Fully integrated with Epic EHR. |
| ZynxOrder by Zynx Health | https://www.zynxhealth.com/solution/zynxorder/ | Provides an extensive library of order sets based on clinical evidence, published guidelines and scientific literature to help physicians in taking clinical decisions. |
| Clinical Exchange ePrescribe NDSC/Change | https://www.changehealthcare.com/clinical-network/clinical-exchange-eprescribe | An electronic prescription application which helps improving patient safety by automatically detecting potential DDIs. |

## 2.4 The need for improving the current Medicine Review process

A few randomized controlled studies evaluated the impact of medicine review on clinically relevant, hard endpoints such as mortality or number of hospitalizations. In the study of Gallagher et al. (2011) 400 hospitalized patients aged more than 65 were randomized to either usual pharmacological care or to medicine review-assisted care and followed for 6 months. Medicine review was delivered by the primary physician by using the START-STOPP criteria and proposed interventions were discussed with the team of attending physicians. While medicine review lowered the number of potential DDIs and inappropriately prescribed drugs it did not impact significantly on major clinical outcomes including all-cause mortality, prevalence of falls or frequency of hospital readmissions. Similarly, the ability of medicine review to significantly reduce inappropriate prescription but not mortality, fall prevalence, and number of hospitalizations was recently confirmed in a RCT on 2008 patients from 110 clusters of inpatient wards from four European countries, who were randomized to receive standard care or a medicine review performed with the support of the STRIPA CDSS (Blum et al., 2021). Likewise, no significant effect of medicine review on the frequency of hospitalization and on patient functional independence and quality of life was observed by Frankenthal et al. (2014), who compared two groups of older adults, residents of a chronic geriatric facility randomized to receive either standard care (n=176) or to medicine review assisted care. The prevalence of falls was, however, significantly lower in the

intervention than in the control group. Results of the SENATOR randomized controlled clinical trial showed no effect on ADR occurrence, all-cause mortality, rehospitalizations and QoL of a medicine review intervention with the support of the SENATOR CDSS (O'Mahony et al., 2020). Similar results were obtained by Pope et al. (2011) and by Zermansky et al. (2006), who observed no effect of medicine review on mortality or emergency hospitalization in older adults staying at continuing-care wards. Medicine review was ineffective in reducing mortality and did not improve QoL also in the community dwelling older adults enrolled in the two RCTs HOMER (Holland et al., 2005) and POLY-Med (Lenaghan et al., 2007). A recent systematic review of the controlled studies on interventions aiming to optimize drug treatment in residential aged care facilities, also including medicine review, showed a significant improvement in drug appropriateness but no apparent effects on hospital admission, falls, ADR, QoL, cognitive function and *Behavioral and Psychological Symptoms of Dementia* (BPSD) (Almutairi et al., 2020).

Collectively, available evidence suggests that, in older adults, medicine review is less effective than expected in preventing drug toxicity, in reducing mortality and in improving QoL. This raises the question of explaining why this tool is not performing well with the final aim of implementing strategies to enhance its efficacy. Doctors' fatigue towards medicine review and poor compliance to its recommendations has been identified as one of the major factors that could explain the limited results of this kind of intervention. However, an additional factor that should be seriously considered is that medicine review is not necessarily directed to very high-risk patients that would benefit of this intervention and that, instead, it is often delivered to low-risk patients that cannot benefit from it (Huiskes et al., 2020). Therefore, the key to improve medicine review efficacy could be a better selection of patients who really need this intervention.

## 2.5 A place for pharmacogenomics in improving medicine review

*Pharmacogenomics* (PGx), the "*study of variations of DNA and RNA characteristics as related to drug response*" (ICH E15, https://www.ich.org/page/efficacy-guidelines), identified a large number of variations in key genes encoding proteins involved in drug PK or *pharmacodynamics* (PD), some of which markedly impact on drug efficacy or safety in the clinics. Consequently, the term *drug-gene interaction* (DGI) has been introduced to emphasize the idea that drug response may change depending on patient genetic status. Traditionally, DGIs have been considered only as interactions in which a specific gene variant enhances or reduces the effect of a certain drug. More recently, the new concept has been proposed that some DGIs may enhance or reduce the propensity of specific patients to experience clinically meaningful DDIs: depending on the genetic background, a certain drug-drug interaction could be either clinically silent or cause serious ADR (Bahar et al., 2017; Verbeurgt et al., 2014). Therefore, at least for some drugs, we should better talk of *drug-drug-gene* interactions (DDGI) than of DDIs. Although this issue has not been deeply investigated in real patients so far, strong theoretical considerations are available in its support.

Different scenarios may be foreseen. A first type of DDGI may occur when blockers of membrane transporters are given to patients with low-function variants of the same transporter: in these conditions a depression of transporter activity much stronger than expected will occur and the efficacy of any other drug

that enters target cells through this transporter will be severely impaired. Many DDGIs may occur at the level of drug metabolism, a complex process that involves several classes of enzymes , each performing different/specific reactions. Genetic variants may occur which impair strongly or only moderately the ability to metabolize certain drugs and confer to the patients a *poor metabolizer* (PM) or an *intermediate metabolizer* (IM) phenotype, whereas other variations may enhance the ability to metabolize certain drugs specifying for the so-called *ultrarapid metabolizer* (UM) phenotype. Among the different metabolizing enzymes, a crucial role is played by cytochrome P 450 (CYP) monooxygenases, which are the key enzymes of the so-called phase I reactions responsible for adding reactive ("functional") groups to drug substrates through oxidoreductive reactions. When a patient bearing a poorly functional variant of an enzyme critically important for the metabolism of a specific drug A will take a second drug B which moderately inhibits this enzyme, drug A metabolism will be severely impaired and drug A toxicity will develop; in other words, because of a DDGI, weak and intermediate drug inhibitors will behave as strong inhibitors when given to patients with specific genetic variants of a metabolizing enzyme. Conversely, when a drug A, which strongly induces the expression of a specific metabolizing enzyme responsible for the degradation of a second drug B, will be given to a patient with a genetic variant that enhances the activity of this enzyme, its effect will be greatly potentiated; consequently, drug B efficacy will be markedly decreased because of its increased degradation and therapeutic failure could occur. In the case of prodrugs, which have to be metabolized to be converted into active products, the consequence of such gene-drug interaction could be an increase in drug effects and the appearance of drug toxicity. Finally, genetic variations may affect the activity/expression of plasma-membrane pumps which extrude large groups of drugs from the cytoplasm and are, therefore, involved in the elimination of pharmacologically active drugs and/or their metabolites in the bile and in the urine. Not differently from what described before about genetic variations affecting drug-metabolizing enzymes, also in the case of pumps it is expected that the functional effects of drugs blocking these pumps or inducing their expression will be enhanced in patients expressing low- and high- activity/expression variants of corresponding genes, who will be at risk, respectively, of drug toxicity or of therapeutic failure.

The idea that the risk of patients to experience severe drug toxicity depends on their genetic background could help explaining the low performance of medicine review observed in the previously-discussed clinical trials. It is tempting to speculate, indeed, that if genetic information is not considered to identify high-risk subjects, the medicine review intervention will be delivered to a large group of low-risk individuals who could not benefit from it. In this perspective, patient genotype, not differently from, for instance, hepatic or renal function, should be included among the critical parameters when evaluating the risk of DDIs and ADR in polypharmacy patients. This would help to better identify high risk patients who may need therapy modifications and, possibly, to increase the prognostic impact of the medicine review process.

## 3. Aim of the study

The aim of the present study was to identify potential DGIs, and more specifically those affecting the susceptibility to develop serious DDIs, in older adults on polypharmacy, from Southern Italy,. Obtaining this

information is essential to perform the pilot study planned in deliverable D8.10 which will focus on the identification of DDGIs in older adults followed as outpatients at FOUND.

In addition, the study also aimed to assess the current availability of CDSS, either purchased or freely available, which incorporate potential DGIs knowledge. This information would be relevant to assess the interest in developing new pharmacogenomic-integrated, IDMP-based CDSS.

## 4. Methods

To identify potentially-relevant DGIs in older adults from Southern Italy, the polymorphic genes that are more likely to be involved in the PK of the drugs taken by these patients, as well the list of drugs that could potentially enhance the effect of the genetic variants of these pharmacogenes, were evaluated.

To identify relevant pharmacogenes, we reviewed drug prescriptions in older adults who underwent medicine review at the Clinical Pharmacology Division of FOUND during the last three years. The population examined consisted in two groups: 1. Patients admitted to the Internal medicine ward, 2. Outpatients followed at the Geriatrics clinic. We considered as relevant those pharmacogenes which encoded enzymes, pumps or transporters involved in the PK of drugs prescribed to more than 5% of the patients of this cohort.

We interrogated major PKG databases including PharmVar (https://www.pharmvar.org/), PharmGKB (https://www.pharmgkb.org), dbSNP (https://www.ncbi.nlm.nih.gov/snp/) and 1000 genomes (https://www.internationalgenome.org/) to retrieve data on the prevalence of the major allele variants of these relevant pharmacogenes in the European population and, when available, in the Italian population and, more specifically in Southern Italy. In addition, we performed a systematic search on *Pubmed* (https://pubmed.ncbi.nlm.nih.gov/) using as key words Italy, Southern Italy, South Italy and the various genetic variants of interest identified with either the rs dbSNP nomenclature or, when available, the star (*) allele designation.

To identify the DGIs in which these pharmacogenes could potentially be involved we reasoned that the effect of *loss of function* or *partial loss of function* gene variants of transporters, drug metabolizing enzymes, or pumps would be significantly amplified and become clinically evident when the patients harboring these gene variants take drugs that inhibit these proteins. Likewise, the effect of drugs that induce their expression would be greatly enhanced in patients harboring gene variants that enhance the activity or the expression of these proteins. Therefore, we looked at the lists of inhibitors and inducers of metabolizing enzymes, transporters and pumps that are freely downloadable from the *DRUGBANK online* website (www.go.drugbank.com) to identify molecules that could interact with variable pharmacogenes giving rise to DGIs. In addition, we interrogated: 1. for CYP inhibitors and inducers, the *Drug Interactions Flockhart Table*™ freely downloadable at the web address https://drug-interactions.medicine.iu.edu/MainTable.aspx (Flockhart et al., 2021) and the Mayo Clinic Pharmacogenomics Association Table (https://www.mayocliniclabs.com/it-mmfiles/Pharmacogenomic_Associations_Tables.pdf), and 2. for the SLCO1B1 transporter, the list published by Karlgren et al. (2012). Tables 2 and 3 report the list respectively of CYP inhibitors and inducers that we used for our analysis whereas Tables 4 and 5 report the list of SCLO1B1 inhibitors and inducers.

The aforementioned lists were cross matched with the list of the drugs taken by older adults at FOUND to sort those drugs that could interact with the previously identified-gene variants to give rise to DGIs. We used the full list of drugs to identify the drugs potentially interacting with variant pharmacogenes and we did not limit our search to the most frequently described drugs, since serious DGIs may occur also with drugs not so frequently prescribed. The result of the described analysis was a list of gene alleles and of potentially interacting drugs whose presence should be assessed (and possibly incorporated in CDSS) when prescribing selected drugs to older adults.

**Table 2** Strong, moderate and weak CYP inhibitors
(*sources: DrugBank Online -https://go.drugbank.com/, the Drug Interactions Flockhart Table ™ -https://drug-interactions.medicine.iu.edu/MainTable.aspx, and the Pharmacogenomic Associations Tables of the Mayo Clinic Laboratories (https://www.mayocliniclabs.com/~/media/it-mmfiles/special-instructions/Pharmacogenomic_Associations_Tables.pdf)*)

| CYP | Strong inhibitors | Moderate inhibitors | Weak inhibitors |
|---|---|---|---|
| **1A2** | Abiraterone, Amiodarone Ciprofloxacin, Enoxacin, Fluvoxamine,Midostaurin, Quinidine, Zafirlukast | Alosetron, Bortezomib, Caffeine, Dosulepin, Gatifloxacin, Imipramine, Ketoconazole, Lidocaine, Mexiletine, Moxifloxacin, Osilodrostat, Simeprevir, Vemurafenib | Anagrelide, Cimetidine, Citalopram, Clascoterone, Conjugated estrogens, Efavirenz, Estradiol, Estradiol acetate, Estradiol benzoate, Estradiol dienanthate, Estradiol valerate, Ethambutol Famotidine, Mefenamic acid, Nevirapine, Opicapone, Ribociclib, Rucaparib, Simeprevir, Tirbanibulin, Tocainide |
| **2B6** | Clotrimazole, Itraconazole, Memantine, Methimazole, Orphenadrine, Raloxifene, Rilpivirine, Ticlopidine | Clopidogrel, Ketoconazole, Sorafenib, Tamoxifen, Thiotepa, Voriconazole | Amprenavir, Clascoterone Crisaborole, Lopinavir, Manidipine, Opicapone, Piperaquine, Simvastatin, , Tirbanibulin |
| **2C8** | Candesartan cilexetil, Clopidogrel, Clotrimazole, Dabrafenib, Erlotinib, Felodipine, Fluticasone, Fluticasone furoate, Fluticasone propionate, Gemfibrozil, Ketoconazole, Mometasone furoate, Ritonavir, Salmeterol, Sorafenib, Trametinib, Zafirlukast | Abiraterone, Amitriptyline, Amlodipine, Bexarotene, Clopidogrel, Clotrimazole, Deferasirox, Diltiazem, Efavirenz, Eltrombopag, Enzalutamide, Fenofibrate, Fluvastatin, Irbesartan, Lenvatinib, Levothyroxine, Loratadine, Lovastatin, Medroxyprogesterone acetate, Nabilone, Nicardipine, Nilotinib, Oxybutynin, Pioglitazone, Quinine, Rabeprazole, Rosiglitazone, Saquinavir, Spironolactone, Tamoxifen, Teriflunomide, Trimethoprim | Amoxicillin, Atazanavir, Belinostat, Bezafibrate, Cabozantinib, Candesartan, Cimetidine, Clascoterone, Idelalisib, Ketoprofen, Lapatinib, Lumasiran, Opicapone, Pazopanib, Pyrimethamine, Quinidine, Rucaparib, Terbinafine, Ticlopidine, Tirbanibulin, Tucatinib, Ubrogepant |
| **2C9** | Capecitabine, Clotrimazole, Delavirdine, Floxuridine, Fluconazole, Gemfibrozil, Miconazole, Nicardipine, Sorafenib, Sulfaphenazole | Abiraterone, Amiodarone, Clotrimazole, Crisaborole, Efavirenz, Felbamate, Fenofibrate, Fluoxetine, Fluvoxamine, Imatinib, Iproniazid, Ketoconazole | Acetyl sulfisoxazole, Aprepitant, Candesartan, Ceritinib, Clascoterone, Ethambutol, Isoniazid, Lopinavir, Mefenamic acid, Olanzapine, Oritavancin, Paroxetine, |

| | | | |
|---|---|---|---|
| | | Metronidazole, , Mifepristone, Nabilone, Quinidine, Sulfinpyrazone, Troglitazone, Valproic acid | Sertraline, Sildenafil, Sulfamethoxazole, Teniposide, Ticagrelor, Ticlopidine, Tirbanibulin, Ubrogepant, Verapamil, Voriconazole, Zafirlukast |
| **2C19** | Chloramphenicol, Clomipramine, Delavirdine, Fluoxetine, Fluvoxamine, Gemfibrozil, Imipramine, Isoniazide, Lansoprazole, Miconazole Stiripentol, Ticlopidine, Tioconazole, Zafirlukast | Abiraterone, Armodafinil, Efavirenz, Eslicarbazepine acetate, Fenofibrate, Ketoconazole, Sertraline, Voriconazole | Amiodarone, Aprepitant, Artenimol, Bortezomib, Cimetidine, Citalopram, Clascoterone, Clozapine, Dexlansoprazole, Esomeprazol, Ethambutol, Etoricoxib, Felbamate, Fenofibrate, Indomethacin, Lonapegsomatropin, Lopinavir, Loratadine, Luliconazole, Manidipine, Memantine, Methadone, Midostaurin, Modafinil, Naloxegol, Nilvadipine, Nilutamide, Olanzapine, Omeprazole, Oritavancin, Oxcarbazepine, Osilodrostat, Pantoprazole, Rucaparib, Rabeprazole, Rotigotine, Sildenafil, Somatotropin, Tipranavir, Tirbanibulin, Topiramate, Ubrogepant, Valproic Acid, Voriconazole, Zonisamide |
| **2D6** | Bupropion, Cinacalcet, Fluoxetine, Paroxetine, Quinidine. Methotrimeprazine, Fluoxetine, Midostaurin, Propafenone, Glycerol phenylbutyrate, Halofantrine, Dacomitinib, Orphenadrine | Abiraterone, Berotralstat Celecoxib, Cimetidine, Chloroquine, Chlorpromazine, Clobazam, Clotrimazole, Clozapine, Cyclosporine, Darifenacin, Delavirdine, Desipramine, Dosulepin, Dronedarone, Duloxetine, Doxepin, Fluvoxamine, Fusidic acid, Halofantrine, Imipramine, Ketoconazole, Lercanidipine, Lorcaserin, Lumefantrine, Manidipine, Metoprolol, Mirabegron, Nicardipine,Nilotinib, Panobinostat, Perhexiline, Pitolisant, Phenylbutyric acid, Primaquine, Quinine, Ritonavir, Rolapitant, Rucaparib, Sulconazole, Sulfaphenazole, Terbinafine, Tipranavir, Tranylcypromine, Venlafaxine, Vilazodone | Amiodarone, Amitriptyline, Amlodipine, Asenapine, Buprenorphine, Celecoxib, Cimetidine, Citalopram, Clascoterone, Clomipramine, Cobicistat, Desipramine, Desvenlafaxine, Diphenhydramine, Entacapone, Epinastine, Escitalopram, Ethambutol, Etoricoxib, Fluphenazine, Gefitinib, Imatinib, Imipramine, Isoniazid, Lansoprazole, Lisdexamfetamine, Lomustine, Loratadine, Lovastatin, Manidipine, Methimazole, Nevirapine, Omeprazole, Oritavancin, Osilodrostat, Ospemifene, Pazopanib, Peginterferon alfa-2b, Pindolol, Primaquine, Proguanil, Propranolol, Rabeprazolo, Ranolazine, Reboxetine, Risperidone, Ritonavir, Rotigotine, Saquinavir, Selegiline, Sertraline, Temsirolimus, Trazodone, Tribanibulin, |

| | | | |
|---|---|---|---|
| | | | Trospium, Ubrogepant, Verapamil, Vemurafenib, Vinblastine, Vinorelbine, Ziprasidone |
| **2E1** | Midostaurin, Miconazole, Tioconazole, Diethylstilbestrol | Isoniazid, Clotrimazole, Alosetron | Ademetionine, Clascoterone, Desipramine, Ethambutol Etoricoxib, Fluphenazine, Itraconazole, Methimazole, Nabilone, Rufinamide, Ticlopidine, Zafirlukast, |
| **3A4/5/7** | Amiodarone, Amprenavir, Atazanavir, Buprenorphine, Ceritinib, Clarithromycin, Cobicistat, Conivaptan, Danazol, Darunavir, Diltiazem, Delavirdine, Econazole, Efavirenz, Elvitegravir, Ergotamine, Idelalisib, Indinavir, Itraconazole, Ketoconazole, Lonafarnib, Loperamide, Lopinavir, Methimazole, Midostaurin, Naloxone, Nelfinavir, Nilotinib, Posaconazole, Ribociclib, Ritonavir, Saquinavir, Stiripentol, Telithromycin, Tipranavir, Troleandomycin, Tucatinib, Voriconazole | Abiraterone, Aprepitant, Berotralstat, Cimetidine, Ciprofloxacin, Clindamycin, Clozapine, Crizotinib, Cyclosporine, Desvenlafaxine, Dronedarone, Erythromycin, Fluconazole, Fluvoxamine, Fosamprenavir, Fosnetupitant, Fusidic acid, Haloperidol, Isavuconazole, Isavuconazonium, Isoniazide, Isradipine, Linagliptin, Lovastatin, Luliconazole, Miconazole, Milnacipran, Netupitant/Palonosetron, Nicardipine, Nilvadipine, Primaquine, Simeprevir, Tioconazole, Venetoclax, Verapamil, Voriconazole, Ziprasidone | Acalabrutinib, Acetaminophen, Alpelisib, Amlodipine, Atomoxetine, Bicalutamide, Bifonazole, , Chlorzoxazone, Citalopram, Clascoterone, Clevidipine, Cyproterone acetate, Dalfopristin, Dasatinib, Dexamethasone, Dexamethasone acetate, Entrectinib, Esomeprazole, Ethambutol, Fluoxetine, Fosaprepitant, Glecaprevir, Glyburide, Grazoprevir, Indinavir, Ivacaftor, Lanreotide, Lapatinib, Lenvatinib, Lesinurad, Lomitapide, Loratidine, Manidipine, Maralixibat, Mirtazapine, Olanzapine, Olaparib, Omeprazole, Oritavancin, Orphenadrine, Osilodrostat, Osimertinib, Palbociclib, Pantoprazole, Pasireotide, Pazopanib, Pexidartinib, Piperaquine, Propofol, Quinidine, Quinupristin, Ranolazine, Remdesivir, Rilpivirine, Rimegepant, Rucaparib, Sarilumab, Siltuximab, Somatostatin, Tacrolimus, Ticagrelor, Tirbanibulin |

**Table 3**. Strong, moderate and weak CYP inducers
(*sources: DrugBank Online -https://go.drugbank.com/, the Drug Interactions Flockhart Table ™ -https://drug-interactions.medicine.iu.edu/MainTable.aspx, and the Pharmacogenomic Associations Tables of the Mayo Clinic Laboratories (https://www.mayocliniclabs.com/~/media/it-mmfiles/special-instructions/Pharmacogenomic_Associations_Tables.pdf)*)

| CYP | Strong inducers | Moderate inducers | Weak inducers | Unknown strength inducers |
|---|---|---|---|---|
| **1A2** | Albendazole, Carbamazepine, Primidone, Rifampicin | Rucaparib | | Insulin, Modafinil, Nafcillin, Omeprazole, Teriflunomide |
| **2B6** | Carbamazepine, Fosphenytoin, Phenobarbital, Nevirapine, Phenytoin | Alpelisib, Rifampicin | Artemether, Esketamine, Isavuconazole, Perampanel, Rifabutin, Ritonavir, Ticagrelor | Dabrafenib, Efavirenz, Letermovir, Roflumilast |
| **2C8** | Phenobarbital, Phenytoin, Rifampicin, Secobarbital | | Avatrombopag, Dabrafenib, Isavuconazole, Quinidine, Rifabutin | |
| **2C9** | Dabrafenib | Alpelisib, Bosentan, Enzalutamide, Rifampicin | Apalutamide, Avatrombopag, Delafloxacin, Isavuconazole, Peginterferon alfa-2b, Warfarin, Ritonavir, Ticagrelor | Carbamazepine, Letermovir, Nevirapine, Phenobarbital, Secobarbital |
| **2C19** | Apalutamide, Rifampicin, Rifamycin, Rifaximin, Rifapentine | Carbamazepine, Enzalutamide, Letermovir, Phenytoin, Rifabutin | | Efavirenz, Norethindrone, Prednisone, Ritonavir |
| **2D6** | | | | Dexamethasone, Oritavancin, Rifampicin |
| **2E1** | | | Delafloxacin, Mitoxantrone Phenobarbital | Isoniazide |

| | | | | |
|---|---|---|---|---|
| **3A4/5 /7** | Apalutamide, Carbamazepine, Clotrimazole, Dexamethasone, Enzalutamide, Fosphenytoin, Lumacaftor, Midostaurin, Mitotane, Pentobarbital, Phenobarbital, Phenytoin, Primidone, Rifampicin, Rifamycin, Rifapentine, Rifaximin, Rimexolone | Bexarotene, Bosentan, Budesonide, Dexamethasone, Dexamethasone acetate, Efavirenz, Etravirine, Modafinil, Nafcillin | Alpelisib, Armodafinil, Artemether, Clobazam, Delafloxacin, Eslicarbazepine acetate, Esketamine, Felbamate, Glycerol phenylbutyrate, Isavuconazole, Lenvatinib, Lesinurad, Modafinil, Nevirapine,Oritavancin, Pexidartinib, Pitolisant, Pyridostigmine, Rifabutin, Rufinamide, Sarilumab, Siltuximab, Tocilizumab, Topiramate, Warfarin | Brigatinib, Dabrafenib, Elagolix, Letermovir, Lorlatinib, Oxcarbazepine, Perampanel, Pioglitazone, Telotristat |

**Table 4**. OATP inhibitors (sources: DrugBank Online, Karlgren et al., 2012*)*

| OATPs | Inhibitors |
|---|---|
| **OATP1B1** | Acetylcysteine, Amprenavir, Artesunate, Asciminib, Atazanavir, Atogepant, Atorvastatin, Axitinib, Beclomethasone dipropionate, Belumosudil, Bempedoic acid, Benzbromarone, Bezafibrate, Brincidofovir, Cabazitaxel, Candesartan, Caspofungin, Cerivastatin, Clarithromycin, Clotrimazole, Cobicistat, Conjugated estrogens, Cyclosporine, Dabrafenib, Daclatasvir, Darolutamide, Darunavir, Diclofenac, Diethylstilbestrol, Digoxin, Dipyridamole, Dovitinib, Dronedarone, Elexacaftor, Eltrombopag, Eluxadoline, Enasidenib, Erythromycin, Estradiol acetate, Estradiol benzoate, Estradiol cypionate, Estradiol dienanthate, Estradiol valerate, Estradiol, Everolimus, Fedratinib, Fexinidazole, Fluticasone furoate, Fluticasone propionate, Fluticasone, Fluvastatin, Fostemsavir, Fusidic acid, Gemfibrozil, Glecaprevir, Idelalisib, Indinavir, Indomethacin, Infigratinib, Irinotecan, Istradefylline, Ivermectin, Ketoconazole, Lenvatinib, Levothyroxine, Lonafarnib, Lopinavir, Lovastatin, Lurbinectedin, Mifepristone, Nelfinavir, Nicardipine, Nifedipine, Nilotinib, Novobiocin, Nystatin, Opicapone, Osilodrostat, Pantoprazole, Paritaprevir, Pazopanib, Pexidartinib, Pibrentasvir, Pioglitazone, Pitavastatin, Pralsetinib, Quinidine, Quinine, Remdesivir, Rifampicin, Rifamycin, Rilpivirine, Rimegepant, Ritonavir, Romidepsin, Rosuvastatin, Roxithromycin, Rucaparib, Sacubitril, Saquinavir, Sildenafil, Simeprevir, Simvastatin, Sirolimus, Sorafenib, Sulfasalazine, Tacrolimus, Telaprevir, Telithromycin, Telmisartan, Teriflunomide, Tipranavir, Tirbanibulin, Ubrogepant, Upadacitinib, Valsartan, Valspodar, Velpatasvir, Venetoclax, Verapamil, Vinblastine, Vincristine, Voxilaprevir |
| **OATP1B3** | Asciminib, Asunaprevir, Ataluren, Atazanavir, Atogepant, Atorvastatin, Baricitinib, Beclomethasone dipropionate, Bempedoic acid, Bortezomib, Cabazitaxel, Clarithromycin, Cobicistat, Cobimetinib, Cyclosporine, Dabrafenib, Daclatasvir, Darolutamide, Dipyridamole, Dovitinib, Dronedarone, Elexacaftor, Enasidenib, Erythromycin, Everolimus, Fedratinib, Fexinidazole, Fluvastatin, Fostemsavir, Gemfibrozil, Glecaprevir, Ibrexafungerp, Idelalisib, Infigratinib, Istradefylline, Ivermectin, Lenvatinib, Levothyroxine, Lonafarnib, Lopinavir, Lurbinectedin, Mifepristone, Nefazodone, Nelfinavir, Novobiocin, Nystatin, Paritaprevir, Pexidartinib, Pibrentasvir, Pioglitazone, Pitavastatin, Pralsetinib, Remdesivir, Rifampicin, Rifamycin, Rilpivirine, Rimegepant, Ritonavir, Romidepsin, Rosuvastatin, Roxithromycin, Rucaparib, Sacubitril, Selinexor, Simeprevir, Sulfasalazine, Telithromycin, Tipranavir, Tirbanibulin, Ubrogepant, Valspodar, Velpatasvir, Vincristine, Voxilaprevir, Telmisartan |

**Table 5** OATP inducers (source: DrugBank Online)

| OATPs | Inducers |
|---|---|
| **OATP1B1** | Taurocholic acid, Cholic acid, Apalutamide |
| **OATP1B3** | Clotrimazole, Progesterone |

# 5. RESULTS

## 5.1 Identification of the drugs most frequently prescribed in geriatric patients at FOUND

As detailed in the methods section, to identify the genes whose variability could potentially be responsible for DGIs in older adults in Southern Italy, we first identified the drugs most prescribed to these patients and then looked for the polymorphic enzymes, pumps and transporters participating to their PK. To achieve the first goal, we reviewed the drug prescription of a total of 369 older adults who underwent medicine review at FOUND: 291 (124 females) of them were patients admitted to the Internal medicine ward and the remaining 78 (35 females) outpatients followed at the geriatric clinics. Median age (IQR) of the patient was 74,0 (69,0-79,0). Table 6 reports the 33 drugs prescribed to more than 5% of patients. Most of them were either cardiovascular drugs, *proton pump inhibitors* (PPIs), for gastroprotection during antiplatelet therapy, or antidiabetic drugs; the list also included allopurinol, a drug for hyperuricemia, tiotropium an anticholinergic drug for *chronic obstructive pulmonary disease* (COPD), rifaximin, an antibiotic frequently prescribed for colonic diverticula, and tamsulosin, an alpha-adrenergic blocker for prostate hyperplasia.

Table 6 reports available data on the main enzymes, pumps and drug transporters involved in the pharmacokinetics of all these 33 drugs. By examining this list, we identified CYP3A4/5, CYP2C9, CYP2C19 and CYP2D6 as the enzymes encoded by polymorphic genes that metabolized most of the drugs in our list of frequently prescribed drugs (33.3% drugs for CYP3A4/5, 18.2% for CYP2C9, 21.2% for CYP2C19 and 15.2% for CYP2D6) and OATP1B1 (SLCO1B1) and PgP/MDR1 (ABCB1) as polymorphic transporter and pump carrying most of them (9.1% for OATP1B1 and 36.4% for ABCB1). We decided to focus specifically on genes encoding CYPs and on SLCO1B1, whereas we did not consider ABC1B1 further, since the role of its genetic variation in drug PK is still controversial and probably small. As described in the next paragraphs, currently-available information on the variability of these polymorphic genes, and on the potential DGIs in which they are expected to be involved in people from Southern Italy were then retrieved.

**Table 6.** Drugs prescribed in more than 5% of geriatric patients at FOUND with the main enzymes, pumps and transporters involved in their pharmacokinetics.

| Drug name | Patients taking the drug (%) | Major degrading enzyme(s) | Major influx/efflux transporter(s) | Major efflux pumps |
|---|---|---|---|---|
| Low dose aspirin | 36.0 | CYP2C9, UGT1A6 | n/a | ABCC4 |
| Furosemide | 30.9 | UGT1A9 | SLC22A6, SLC22A8 | ABCC4 |
| Atorvastatin | 30.1 | CYP3A4/5, UGT1A1, UGT1A3, UGT2B7 | SLCO1B1 | ABCC2, ABCB1 |
| Ramipril | 20.3 | CES | SLC15 | n/a |
| Clopidogrel | 19.8 | CYP2C19, CYP2C9, CYP3A4, CES1 | n/a | ABCB1 |
| Allopurinol | 17.6 | AOX1, XDH | SLC22A11, SLC22A12 | ABCG2 |
| Carvedilol | 16.3 | CYP2D6 | n/a | ABCB1, ABCC2 |
| Amlodipine | 16.3 | CYP3A4 | n/a | ABCB1 |
| Hydrochlorothiazide | 16.0 | Not metabolized | n/a | n/a |
| Pantoprazole | 15.7 | CYP2C19, CYP3A4 | n/a | ABCB1, ABCG2 |
| Insulin glargine | 15.2 | IDE | n/a | n/a |
| Metformin | 14.4 | Not metabolized | SLC22A1/A2, SLC47A1/A2 | ABCB1, ABCG2 |
| Bisoprolol | 13.6 | CYP3A4 | n/a | n/a |
| Esomeprazole | 12.2 | CYP2C19, CYP3A4 | n/a | ABCB1 |
| Warfarin | 10.3 | CYP2C9 CYP3A4 | n/a | ABCB1 |
| Omeprazole | 10.0 | CYP2C19 | n/a | ABCB1 |
| Spironolactone | 9.8 | FMO, CES, TMT, CYP3A4 (minor) | SLCO1A2 | n/a |
| Insulin lispro | 9.5 | IDE | n/a | n/a |
| K- canrenoate | 9.2 | IDE | n/a | n/a |
| Tiotropium | 9.2 | CYP2D6, CYP3A4 | n/a | n/a |
| Olmesartan Medoxomil | 8.7 | Plasma esterases | SLCO1B1 | ABCB1 |
| Digoxin | 8.4 | Mainly excreted as unchanged drug | n/a | ABCB1 |
| Simvastatin | 8.4 | CYP3A4/5, | SLCO1B1 | ABCC2, ABCB1 |
| Irbesartan | 8.1 | CYP2C9 | n/a | ABCB1 |
| Tamsulosin | 7.3 | CYP3A4, CYP2D6 | n/a | n/a |

| | | | | |
|---|---|---|---|---|
| Nitroglycerin | 6.0 | ALDH2 | n/a | n/a |
| Rosuvastatin | 6.0 | CYP2C9 | SLCO1B1 | ABCB11 |
| Rifaximin | 6.0 | CYP3A4/5 | n/a | ABCB1 |
| Insulin aspart | 5.7 | IDE | n/a | n/a |
| Nebivolol | 5.7 | CYP2D6 (minor) | n/a | n/a |
| Ursodeoxycholic acid | 5.7 | BAAT | SLCO1A2 | ABCB11 |
| Doxazosine | 5.4 | CYP3A4 | n/a | n/a |
| Folic acid | 5.1 | FOLH1 | SLC19A1, SLC46A1, SLC25A32 | ABCC1, ABCC2, ABCC3, ABCC4, ABCG2, ABCB1 |

ABBREVIATIONS: ALDH2: Aldehyde Dehydrogenase 2; AOX1: Aldehyde Oxidase 1; BAAT: bile acid coenzymeA:aminoacidN-acyltransferase; CES: carboxylesterase; FMO: flavin mono-oxigenase; FOLH1: Folate Hydrolase 1; IDE: Insulin-degrading enzyme; TMT: Thiol S-methyltransferase; UGT: UDP-glucuronosyltransferase; n/a: no information available

## 5.2 Drug-gene interactions involving members of the CYP3A subfamily

CYP3A4, CYP3A5, CYP3A7, and CYP3A43 belong to a subfamily of closely related CYPs, which are encoded by genes located in a 231 kb gene cluster on the q21–22 locus of chromosome 7 (Finta and Zaphiropoulos, 2000).

CYP3A4 ranks first among CYPs for the number of metabolized drugs since it metabolizes about 30% of the approved drugs in humans (Zanger and Schwab, 2013). This 57 KDa protein consists of 503 amino acids and is mainly expressed in the liver and in the gut (https://www.genecards.org/cgi-bin/carddisp.pl?gene=CYP3A4). CYP3A4 exists in several isoforms all generated by differential splicing of the same 13 exon (https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=DetailsSearch&Term=1576); interestingly, in few minor isoforms intergenic trans-splicing occurs with the neighbour CYP3A4 exon 1 (Finta and Zaphiropoulos, 2002).

CYP3A5 is 52.5-kDa, 502 amino acid protein encoded by a nine-exon gene located in the CYP3A locus; CYP3A5 has an 84% similarity in protein sequence with CYP3A4 and a large but not complete overlap in substrate specificity with this cytochrome (Wrighton and Stevens, 1992); differences in catalytic mechanisms and in regioselectivity have been reported as well (Emoto and Iwasaki, 2006). While CYP3A4 is predominantly expressed in the liver and in the gut, CYP3A5, which is also expressed in these organs, is the predominant CYP3A form in extrahepatic tissues. The expression of the third member of the CYP3A family, CYP3A7, is limited to foetal life and this cytochrome does not seem to be significantly involved in drug metabolism after birth (Komori et al., 1990).

### 5.2.1 Main haplotypes-and diplotypes of CYP3A4 and their prevalence in Europe

There is a high interindividual variability in the expression and activity of CYP3A4 in the liver (Rodriguez-Antona et al., 2005; Zanger and Schwab, 2013). Even though enzyme activity has a unimodal distribution in the population, arguing against a major contribution of gene polymorphism, studies in twins showed that the CYP3A4 activity pattern is highly heritable, and it has been estimated that heritability accounts for 66-88% of interindividual variability in CYP3A4 activity (Penno et al., 1981). This discrepancy between the heritable variability in CYP3A4 activity and the lack of a clear multimodal pattern represented for a long time a real conundrum, which was designated the “missing heritability problem” (Klein and Zanger, 2013). Several explanations have been proposed to clarify this point. Briefly, new CYP3A4 gene polymorphisms of low prevalence but high functional impact (e.g., CYP3A4*22) have been identified. In addition, a role has been identified in determining CYP3A4 activity for other polymorphic genes including CYP3A5, which has an overlapping enzyme activity, and genes encoding for proteins which regulate CYP3A4 expression or activity such as P450 oxidoreductase and peroxisome proliferator-activated receptor alpha (Klein and Zanger, 2013).

At the time of writing, 35 alleles have been identified for CYP3A4 (https://www.pharmvar.org/gene/CYP3A4), most of which have a low prevalence in many populations and limited or no functional effect on enzyme expression or activity (Lamba et al., 2002). On Sept 26, 2017, the CYP allele classification was moved to the *PharmVar* web site and major changes were

introduced in the reference “normal” allele, CYP3A4*1. While, indeed, previously, only the CYP3A4*1A variant was considered as “normal” and the *1B suballele, which differs from it for an A>G transition at position -392 (rs2740574, g.-392A>G), as a benign variant with no major functional consequences (Westlind et al., 1999; Ball et al., 1999; García-Martín et al., 2002; Spurdle et al., 2002; Wojnowski and Kamdem, 2006), now they are classified both as ”normal” and designed as CYP3A4*1001 (formerly *1B) and CYP3A4*1002 (formerly *1A) (https://a.storyblok.com/f/70677/x/0e7eec276a/gene-info_cyp3a4_v1-0.pdf). According to the 1000 genomes database the prevalence of CYP3A4*1001 (the G, reference, allele) in the European population, is 97.22 (https://www.internationalgenome.org/). The previously identified CYP3A4*1 suballeles *1C, *1D, *1F, *1H, *1J-L, *1N, *1P-S were cancelled from the new *PharmVar* classification. Among the other CYP3A4 alleles, CYP3A4*1G, CYP3A4*20 and CYP3A4*22, are those that have been more deeply investigated (Werk and Cascorbi, 2014). CYP3A4*1G (rs2242480; g.99361466C>T; c.1026+12G>A intron 10 variant) occurs in its variant form T in about 8% of the European population (as diplotype: 1% homozygous and 14% heterozygous). Its functional consequences are still unclear, though evidence has been reported that it could decrease the clearance of important drugs such as atorvastatin, cyclosporin and fentanyl (Dong et al., 2012; Gao et al., 2008; Hu et al., 2006). The CYP3A4 *20 allele contains the rs67666821 insertion/deletion (indel), which may occur either by the deletion of a T in a TTTTT sequence in the coding region of exon 13 (in isoform 1: c.1461del, p.Lys487fs; in isoform 2: c.1458del, p.Lys486fs), or by the insertion of an additional T (in isoform 1: c.1461, p.Pro488fs; in isoform 2: c.1458dup, p.Pro487fs); the consequence of this change is a frameshift leading to the synthesis of a truncated protein and the complete loss of CYP3A4 activity (Gómez-Bravo et al., 2018; Levran et al.,2013; Lloberas N et al., 2018; Westlind-Johnsson et al., 2006). In non-Finnish Europeans the del variant has a prevalence of 1% and the ins variant of 4% (https://gnomad.broadinstitute.org/). The estimated prevalence of these indels is even lower in the ALFA database (del: 0%; ins 1%) (https://www.ncbi.nlm.nih.gov/snp/docs/gsr/alfa/). Additional CYP3A4 frame shift allele variants with a much lower prevalence have been described, including CYP3A4*6 and CYP3A4*26. Westlind-Johnsson et al. (2006) estimated the prevalence of the CYP3A4 *20 allele to be less than 0.06% in white subjects based both on sequence data form 428 German individuals and on published data.

The CYP3A4*22 allele was first described in 2011 (Wang et al., 2011) and its identification represented a major advancement for the understanding of the CYP3A4 “missing heritability problem”. As matter of fact, this variant *per se* accounts for about 12% of the variability in CYP3A4 activity. The CYP3A4*22 allele contains the intronic SNP rs35599367 (g.15389C>T-intron 6), which causes a significant decrease in enzyme activity by altering RNA splicing (Wang and Sadee, 2016). This CYP3A4 allele is mainly observed in Europeans and admixed Americans whereas its prevalence is much lower in Asiatics and Africans. According to the *1000 genomes database*, in the European population the prevalence of the variant CYP3A4*22, rs35599367 reduced activity allele A is 5%. At the genotype level, 0.2% of the population is homozygous for the low activity allele A, and 9.5% is heterozygous (https://www.internationalgenome.org/).

Additional missense variants with reduced enzymatic activity have been identified including CYP3A4*8, *11, *13, *16 and *17 but their prevalence is negligible.

### 5.2.2 Prevalence of CYP3A4 haplo- and diplotypes in Italy

Only limited information is available on the prevalence of CYP3A4 alleles in Italy. Data from the *Tuscans in Italy* cohort of the 1000 genome project reports a prevalence of 97.2% for CYP3A4*1001. In the same cohort, the prevalence of the variant T allele of rs2242480 (*1G) was 8.4%, whereas the heterozygous diplotype CT was detected in 16.8% of tested people. No data is available in the same database on the nonfunctioning allele rs67666821 (*20), which, however, was not detected in any of the 478 Italian individuals tested by Apellániz-Ruiz et al. (2015). For the rs35599367 (*22) allele, a prevalence of 3.7 % for the minor, reduced activity A allele and of 7.5% for the heterozygous genotype (AG) was reported in the *Tuscans in Italy* cohort of the 1000 genome project. Magliulo et al. (2011) measured the prevalence of the main CYP3A4 (and CYP3A5) alleles in a series of 54 outpatients affected with Alzheimer disease and 254 normal controls, all recruited at the Ospedale Maggiore della Carità, in Novara, Northern Italy: the prevalence of the CYP3A4*1002 was 1.9% in patients and 3.6% in controls whereas only 0.9% of patients and 0.7% of controls showed the *3 allele and none the *4. Caruso et al. (2014) reported that 6% of a small cohort of 50 epileptic patients from Southern Italy were heterozygous for *22 (*1/*22) whereas none was homozygous for this allele.

In conclusion, although genetic variation is commonly considered not to represent a significant issue for CYP3A4, available data suggest that more than 5% of the Italian population have at least one low-functioning allele of this cytochrome.

### 5.2.3 Main haplotypes-and diplotypes of CYP3A5 and their prevalence in Europe

CYP3A5 is a highly polymorphic cytochrome (Daly, 2006). At the time of writing, 9 star alleles have been described for CYP3A5 with multiple suballeles (https://www.pharmvar.org/gene/CYP3A5). Among them *1 is the normal variant whereas *3 (rs776746, g.12083A>G causing a splicing defect), *6 (rs10264272, g.19787G>A causing a splicing defect) and *7 (rs41303343, g.32228dup, p.T346fs) are non-functional since they all cause the formation of truncated proteins; the functional consequences of the remaining star allele variants is still uncertain. The combination of CYP3A5 alleles in diplotypes defines different metabolizer phenotypes. Specifically, *1/*1 is found in *normal metabolizers* (NM), *1/3, *1/*6 and *1/*7 in *intermediate metabolizers* (IM) and *3/*3.*6/*6, *7/*7, *3/*/6, *3/*7 and *6/*7 in PM. Remarkably, in the European population, the prevalence of the normal *1 allele is only 7.4% whereas the most represented allele is the non-functional variant *3 which, according to the 1000 genomes database, has a prevalence of 94%; at the diplotype level, the *3/*3 homozygous has a prevalence of 89.1% and the *1/*3 heterozygous of 10.5% (the 1000 genomes project, https://www.internationalgenome.org/). In the same database, the non-functional *6 variant has an allele prevalence in Europeans of 0.3%; at the diplotype level, *6 occurs in heterozygosity in 0.6% of the population. The important consequence of these data is that in most of the Europeans, CYP3A5 is non-functional or minimally functioning. Therefore, differently from what usually happens in pharmacogenomics, clinical consequences will arise

when the “normal” reference allele and not the variant allele will be expressed since this will cause a higher than “normal” metabolism of CYP3A4/CYP3A5 substrates because of the overlapping specificity of these two CYPs. The clinical consequences of this phenomenon have been demonstrated, for instance, in patients taking with the immunosuppressant drug tacrolimus, who, if expressing CYP3A5*1, need higher than normal doses of this drug (Barry and Levine, 2010).

### 5.2.4 Prevalence of CYP3A5 haplo- and diplotypes in Italy

The 1000 genome project reports data on the CYP3A5*3 alleles in the *Tuscans in Italy cohort*, which is composed essentially of people from Central Italy; 89.7% of people from this group were *3/*3 homozygous and 10.3% *1/*3 heterozygous with no *1/*1 homozygous. Data on people (mostly) from Northern Italy are reported in few additional small published series. Stratta et al. (2012) genotyped 143 patients who underwent kidney transplantation at the Amedeo Avogadro University-Maggiore Hospital of Novara, in Northern Italy. Also in this series, no *1/*1 homozygous were identified whereas most of the patients were *3/*3 homozygous (88,8%) and 11% of them were *1/*3 heterozygous (Stratta et al., 2012). Likewise, only one *1/*1 patient was identified in a cohort of 92 young kidney transplant recipients from Milan, in Northern Italy, whereas 80% of patients were *3/*3 homozygous and 20.7% *1/*3 heterozygous (Ferraresso et al., 2011). In the study of Magliulo et al. (2011) the prevalence of CYP3A5*3 was 88.9% in Alzheimer patients and 93.3% in normal volunteers. The only published study on CYP3A5 alleles in Southern Italy evaluated a cohort of 101 patients (70.6% from Sicily), who underwent liver or kidney transplantation; in this patient group the prevalence of the *3/*3 and *1/*3 genotypes was respectively 84.9% and 13.8% with only 1.3% of the patients showing the *1/*1 fully functional diplotype (Provenzani et al., 2011).

### 5.2.5 Potential DGIs involving CYP3A4 and CYP3A5 gene variants

As mentioned already before, CYP3A4 is the cytochrome that metabolizes the highest number of drugs in humans and CYP3A5 (when expressed) has a large substrate overlap with it. In addition, not only these cytochromes may be blocked by the inhibitors listed in Table 2, but their genes are also inducible by a long list of compounds (Zanger and Schwab, 2013; Table 3). Although genetic variability has been classically considered to be minor with these cytochromes, a few CYP3A4 alleles (namely *1G and, more importantly, *22), which occur in a small but not negligible percentage of people, may impair CYP3A4 activity whereas the presence of the “normal” CYP3A5 *1 allele strongly increases the metabolism of CYP34/CYP3A5 substrates. Though occurring only rarely, CYP3A4/5 polymorphisms may significantly alter the response to clinically relevant drugs (Saiz-Rodríguez et al., 2020). Importantly, because of the overlapping substrate specificity of CYP3A4 and CYP3A5, the metabolizer phenotype will be the result of the combination of the genotypes of these two cytochromes. More specifically, the following genotype to phenotype relations can be identified:

1. CYP3A4/5 PM: people with the CYP3A5*3/*3 genotype and carriers of at least one CYP3A4*22 allele;

2. CYP3A4/5 IM: individuals with either CYP3A4*1/*1 and CYP3A5 *3/*3 or CYP3A5*1/*1 or CYP3A5 *1/*3 plus at least one CYP3A4 *22 allele;
3. CYP3A4/5 EM: people with a CYP3A5 *1/*1 or CYP3A5 *1/*3 and CYP3A4 *1/*1 genotype).

Gene variants in CYP3A4/5 may alter drug metabolism and efficacy of many drugs some of which have a central role in geriatric pharmacotherapy such as, for instance, statins. Indeed, patients carrying the CYP3A4*22 allele showed a higher clinical response to atorvastatin, lovastatin and simvastatin (Elens et al., 2011a; Wang et al., 2011). Kitzmiller et al. (2013) showed that significantly lower statin doses were required to achieve optimal lipid control in poor CYP3A4/5 metabolizers and in IM than in extensive metabolizers. The effect of the other CYP3A4 polymorphisms on statin metabolism is not well established, but several reports suggest that CYP3A4*1001 (formerly *1B) (Kajinami et al., 2004) and CYP3A4*1G (Gao et al., 2008) could be associated to a higher clinical response to atorvastatin. Other drugs whose metabolism and clinical effects are considerably affected by CYP3A4/5 genetic variation but that are less frequently prescribed in older adults than statins, are the immunosuppressants cyclosporine, tacrolimus and everolimus (Elens et al., 2011b; Elens et al., 2012; Gómez-Bravo et al., 2018; Hesselink et al., 2003; Lloberas et al., 2018), benzodiazepines and in particular midazolam (Miao et al., 2009), the opioid methadone (Levran et al., 2013), and the anticancer drug tamoxifen (Sanchez Spitman et al., 2017). The impact of CYP3A5 genotype on immunosuppressant drug plasma concentrations may be of major clinical relevance in patients undergoing organ transplantation and in 2015 the Clinical Pharmacogenetics Implementation Consortium (CPIC) issued a dedicated guideline for dose adjustment of tacrolimus according to CYP3A5 genotype (Birdwell et al., 2015).

Besides directly affecting the metabolism of CYP3A4/5 substrates, gene variants of these two cytochromes may be involved in DGIs that modify the susceptibility to severe DDIs. It is expected, indeed, that when CYP3A4 inhibitors (also including moderate or weak inhibitors) are given to patients with non-functional CYP3A4 alleles (e.g., CYP3A4*22), they will further suppress an already deficient enzyme activity and increase the toxicity of drugs normally metabolized by this cytochrome. Likewise, the effect of CYP3A4/5 inducers are expected to be stronger in patients with the CYP3A5*1 allele since they will further potentiate the metabolizing activity of patients who are already extensive metabolizers. Based on the data on CYP3A4*22 and CYP3A5*1 prevalence in Southern Italy, it is expected that DGIs that could increase the risk of DDIs could roughly occur in 1-5% of the patients from this region, also including geriatric patients. By cross matching the lists of the drugs most frequently prescribed to geriatric patients at FOUND with the list of CYP3A4 inhibitors (Table 2), we identified the antiarrhythmic drug amiodarone, the calcium channel blockers diltiazem and verapamil and the two PPIs, omeprazole and pantoprazole as the drugs that, in geriatric patients, could most likely be responsible for DGIs involving CYP3A4 variant alleles. Although about 10% of the population from Southern Italy is expected to be heterozygous for CYP3A5*1 and 1% homozygous and should, consequently, be highly sensitive to CYP3A4/5 inducers, we did not find any of such drugs among those commonly prescribed to older adults at FOUND.

## 5.3 Drug-gene interactions involving CYP2C9

CYP2C9 is a 490 amino acid protein with a molecular weight of 55.6 kDa, mainly expressed in the gut and in the liver, where it represents about 20% of CYPs (https://www.proteinatlas.org/ENSG00000138109-CYP2C9; Wang et al., 2009). This enzyme is encoded by a nine-exon gene located in the CYP2C locus of the long arm of human chromosome 10 (q23.33), which also includes the genes encoding CYP2C8, 2C18 and 2C19 (Gray et al., 1995). CYP2C9 participates to the metabolism of 12.8 % of all approved drugs (Wang et al., 2009; Zanger et al. 2013). Its substrates include selected members of relevant drug classes, such as sulfonylureas, nonsteroidal anti-inflammatory drugs, COX2 inhibitors, diuretics, antiepileptics, angiotensin II receptor inhibitors, anticancer drugs, and anticoagulants (Zanger and Schwab, 2013). The CYP2C9 gene is highly variable and, because of its relevance in drug metabolism, it is listed among VIPs (https://www.pharmgkb.org/vips).

### 5.3.1 Main CYP2C9 haplotypes-and diplotypes and their prevalence in Europe

At the time of writing, the PharmVar database includes 71 CYP2C9 alleles and, for some of them, several suballeles (https://www.pharmvar.org/gene/CYP2C9). Most of them are *single nucleotide variants* (SNVs), but *copy number variants* (CNVs) have also been described (Botton et al., 2019). CYP2C9*1 is the normal function allele whereas *2, *4, *5, *8 and *11 are intermediate activity variants, and *3 and *6 are loss of function variants (Kirchheiner et al., 2005). The mechanism responsible for the observed change of activity has been determined for selected alleles (reviewed in Wang et al., 2009). For instance, in CYP2C9*2 (rs1799853, c.430C>T) a missense SNV occurs because of the change of an arginine with a cysteine in position 144 (p.Arg144Cys); this amino acid change impairs the interaction of CYP2C9 with NADPH-dependent cytochrome P450 oxido-reductase. In CYP2C9*3 (rs1057910, c.1075A>C) there is Ile359Leu substitution in the substrate recognition site 5, which significantly reduces the affinity of the enzyme for its substrates. CYP2C9*6 (rs9332131) is an indel variant (c.818del; c.818dup) causing frameshift (p.Lys273fs and p.Glu274fs, respectively for the insertion and the deletion) with the production of a truncated, non-functional protein.

In the European population, CYP2C9*1, the “normal”, reference allele, is the more represented CYP2C9 variant with a prevalence of 79.33% followed by *2 (12.73%) and *3 (7.55%). The *8 (0.0018) and *11 (0.0016) variants are much less represented and the prevalence of *5 and *4 is negligible (https://www.pharmgkb.org/). The combination of haplotypes in diplotypes specifies for different CYP2C9 metabolizer phenotypes: NM (*1/*1), IM (such as *1/*2, *1/*3, *2/*2) and PM (e.g., *2/*3, *3/*3). In the European population, CYP2C9 *1/*1 and *1/*2 are the most frequently observed diplotypes, accounting for 62.9 and 20.2% of the total. The PM diplotypes *3/*3 and *6/*6 are much less prevalent occurring with a prevalence of 0.57 and $7{,}8510^{-06}$ %, respectively (https://www.pharmgkb.org/). These data indicate that most of the CYP2C9 variability in Europe involves a partial reduction of enzyme activity.

### 5.3.2 Prevalence of CYP2C9 haplo- and diplotypes in Italy

Few studies assessed the prevalence of CYP2C9 alleles in the Italian population. In the *Tuscans in Italy cohort* of the 1000 genome project, the prevalence of CYP2C9*3 was 8.4%, corresponding to 0.9% homozygous and 15% heterozygous (https://www.internationalgenome.org/). Scordo et al. (2002) studied a small cohort of 93 patients from Northern Italy receiving chronic warfarin anticoagulant therapy. In this series the prevalence of CYP2C9*2 and *3 was, respectively, 12.4% and 12.9%. Fifty-four patients (58.06%) showed the wild-type diplotype*1/*1, whereas 31 (33.3%) showed one muted and one wild-type allele (*1/*2, n 15; *1/*3, n 16), and 8 (8.6%) with two mutated alleles (*2/*2, n 2; *3/*3, n 2; *2/*3, n 4). Margaglione et al. (2000) genotyped a cohort of 88 patients from Southern Italy and found a prevalence of 48.9% for CYP2C9*1, 35.6% for the CYP2C9*2 haplotype, 16.7% for the CYP2C9*3 haplotype; at the genotype level, 35.6% of the patients were *1/*2 heterozygous (IM), 15.5% *1/*3 heterozygous (IM), 1.1% *3/*3 homozygous (PM) and 1.1% *2/*3 (PM) double heterozygous. Similar prevalence data have been observed in later studies. For instance, Spreafico et al (2003) showed that, in a cohort of patients from Northern Italy, the allele frequencies for CYP2C9*1, *2 and *3 were respectively, 78%, 13% and 9%. Likewise, in 266 patients from Southern Italy studied by Mazzaccara et al. (2013) the prevalence of CYP2C9*1, *2 and *3 was 77.5%, 15.7% and 9.8% respectively; *1/*1 and *1/2 were the most frequent diplotypes being observed in 60.2% and 22% of the study population, respectively. About 1.1% of the sample showed the PM *3/*3 diplotype whereas the IM diplotypes *1/*3, *2/*2 and *2/*3 occurred in 12.5%, 2.3% and 1.9% of the patients. Carano et al. (2017) used the *analysis of molecular variance* (AMOVA) to compare the prevalence of CYP2C9 alleles in people from Northern, Central and Southern Italy and did not find significant differences. To summarize, available evidence suggests that about 20% of the Italian population may have a CYP2C9 activity lower than normal, with no major differences among different regions.

### 5.3.3 Potential DGIs involving CYP2C9 gene variants

Genetic variation of CYP2C9 may significantly alter clinical response to selected members of major drug classes, some of which frequently prescribed in the elderly. More specifically, in people with CYP2C9 variants marked may occur changes in pharmacokinetics and efficacy of the oral anticoagulant warfarin, some NSAIDs and some antiepileptic drugs. CPIC issued specific recommendations for dosage adjustment of these drugs according to the CYP2C9 genotype (Karnes et al., 2021; Johnson et al., 2017; Theken et al., 2020). Warfarin is an oral anticoagulant drug, still frequently used in older adults with atrial fibrillation. Warfarin is degraded to the inactive metabolite 7OH-warfarin by CYP2C9 and, therefore, warfarin concentrations will be higher than normal in CYP2C9 PMs and IMs who will be at high risk of hemorrhages. Genotype-guided dose adjustment of warfarin represents one of the prototypical examples of precision therapy in pharmacogenomics and involves the analysis of the variants also of two other genes besides CYP2C9, CYP4F2 and vitamin K epoxide reductase complex subunit 1. CYP4F2 converts reduced vitamin K to hydroxy-vitamin K1, and vitamin K epoxide reductase complex subunit 1 regenerates epoxidized vitamin K1. In addition, in African Americans, rs12777823, a SNP

located in the CYP2C cluster, outside the CYP2C9 gene but near the CYP2C18 gene, is associated to increased warfarin levels requiring dose reduction (Johnson et al., 2017). Warfarin dose adjustment is usually performed by using dosing algorithms which not only include the aforementioned genes, but also evaluates interacting drugs and food (http://www.warfarindosing.org/Source/References.aspx#). Among NSAIDs, celecoxib, flurbiprofen, ibuprofen, and the oxicams lornoxicam, meloxicam, piroxicam and tenoxicam are those more severely affected and included in the CPIC guidelines. PM and IM (especially those with more severe reduction of enzyme activity) are expected to have higher drug exposures and this effect is stronger for long half-life drugs such as piroxicam and meloxicam. Accordingly, in PM, the CPIC guidelines recommend starting therapy with 25-50% of the lowest starting dose in the case of the short half-life drugs celecoxib, flurbiprofen and ibuprofen, whereas drugs with long half-life drugs such as meloxicam, tenoxicam or piroxicam must be avoided (Theken et al., 2020).

Not only CYP2C9 gene variants may alter the metabolism of drugs used in geriatrics, but they may also be involved in DGIs that increase the risk of DDIs. Specifically, similarly to what described for CYP3A4, CYP2C9 inhibitors (also including those classified as moderate and weak) will further increase the already low CYP2C9 enzyme activity in PMs or IMs and increase the plasma concentration of their substrates, up to toxic levels in some cases. By cross checking the lists of CYP2C9 inhibitors (Table 2) with the list of the drugs prescribed to older adults at FOUND, we identified amiodarone, fenofibrate, paroxetine, sertraline as the potential culprits of these DGIs. Considering that only about 80% of the Italian population is CYP2C9 NM (CYP2C9*1/*1) with the remaining being either IM or PM, DGIs involving CYP2C9 could theoretically be observed in about 20% of patients also including older people attending to geriatric outpatient clinics. Noteworthy, no major differences have been observed among the different Italian macroareas and, therefore, these prevalence estimates may also apply to older adults from Southern Italy.

## 5.4 Drugs interacting with CYP2C19

CYP2C19 is a 490-amino-acid monooxygenase encoded by a nine-exon gene located in the CYP2C9 locus on chromosome 10q23.33, which also contains the CYP2C8, CYP2C9 and CYP2C18 genes (https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=DetailsSearch&Term=1557). CYP2C19 is mainly expressed in the gut and in the liver whereas it is not detectable in the brain or in cells of the immune system (https://www.proteinatlas.org/ENSG00000165841-CYP2C19). CYP2C19 has an important role in the metabolism of polyunsaturated fatty acids (Lucas et al., 2010) and is involved in the metabolism of about 7% of all approved drugs in humans including members of clinically relevant drug families such as PPIs, antiepileptic drugs, tricyclic antidepressants, β-blockers and benzodiazepines (Zanger and Schwab, 2013). The first indication of the high interindividual variability in CYP2C19 activity emerged 40 years ago studying mephenytoin and, nowadays, CYP2C19 is classified among VIPs by PharmGKB (https://www.pharmgkb.org/vips).

### 5.4.1 Main CYP2C19 haplotypes-and diplotypes and their prevalence in Europe

At the time of writing, thirty-nine CYP2C19 alleles have been registered in the *PharmVar* database and some of them have multiple suballeles (https://www.pharmvar.org/gene/CYP2C19; Botton et al., 2021). According to the data reported in the *PharmGKB* database, the normal function allele CYP2C19*1 variant is the most abundantly expressed in the European population and its prevalence is 62.47%; among the other ten most represented alleles CYP2C19*2, *8, *4, *3 and *6 are loss of function variants with a prevalence respectively of 14.66%, 0.34%, 0.20%, 0.17% and 0.03%; these prevalence data imply that more than 15% of CYP2C19 alleles in the European population are non-functional. The *9 allele is an intermediate activity variant with a low prevalence in Europe (0.07%); even lower is the prevalence of the other intermediate activity alleles (*10, *16 and *19), none of which ranks in the first ten more prevalent CYP2C19 variants in the European population. The *17 allele is a hyperfunctioning variant causing an ultrarapid metabolizer (UM) phenotype (Sim et al., 2006); two SNPs are contained in the CYP2C19*17 variant, one in the promoter (-806C>T) and the other in the coding sequence (80161A>G; I331V). The SNV in the promoter region enhances gene transcription accounting for increased enzyme activity. CYP2C9*17 ranks second for prevalence in Europe accounting for 21.6% of all the CYP2C19 alleles.

The diplotypes arising from the combination of these haplotypes specify for different phenotypes: according to the CPIC classification (https://cpicpgx.org/; Scott et al., 2013), individuals with the *1/*1 diplotype are extensive (i.e., normal) metabolizer (EM), those with *17/*17 and the *1/*17 diplotypes are UM whereas the *1/*2, *1/*3, *2/*17 diplotypes specify for IM, and the *2/*2, *2/*3, *3/*3 diplotypes for PM. Thirty-nine percent of the Europeans have the EM diplotype *1/*1, 27% and 4.68% the UM diplotypes *1/*17 and *17/*17, respectively. The PM diplotype *2/*2 is found in 2.15% of the individuals and the intermediate metabolizer *1/*2 in 18.3%. To summarize, diplotypes with "*altered*" function are highly prevalent in Europe, being found in at least 30% of individuals.

### 5.4.2 Prevalence of CYP2C19 haplotypes- and diplotypes in Italy

Few studies have investigated the prevalence of the different CYP2C19 haplotypes and diplotypes in the Italian population. In a group of 360 volunteers from Southern Italy, Scordo et. al (2004) found a prevalence of 88.9% for the wild type CYP2C19*1 allele and of 11.1% for the loss of function *2 allele; no other variants were identified in this small population; the most prevalent diplotype was *1/*1 (79.4%) whereas the homozygous *2/*2 and the heterozygous *1/*2 were observed only in 1.7% and 18.9% of the subjects. Giusti et al. (2007) assessed CYP2C19 genotype in 1419 patients mostly from Central Italy; in this group the prevalence of the *1/*1 *1/*2 *2/*2 diplotypes was 68.6%, 28.6%, and 2.8%, respectively. The most prevalent CYP2C219 diplotype was *1/*1 (42.5%) also in a cohort of 47 women with breast cancer from the *Italian Tamoxifen Prevention Trial,* followed by the intermediate activity diplotype *1/*2 (24.3%) (Serrano et al., 2011). In this study, the prevalence of diplotypes containing the high activity CYP2C19*17 variant was 3.8% for the homozygous *17/*17, and 23.2% and 4.4% for the

heterozygous *1/*17 and *2/*17. In a cohort of 90 healthy subjects from different Italian regions, Caccamo et al. (2013) found a prevalence of 80.3% for EMs (*1/*1), 16.7% for IMs (*1/*2) and 3% for PMs (*2/*2). The comparative study by Carano et al. (2017) on CYP allele frequency in different Italian macroareas showed significant differences for CYP2C19 among Northern, Central and Southern Italy. More specifically, while in the population from Southern Italy, 87.3% of the individuals showed the*1/*1 diplotype, 12.7% the IM *1/*2 diplotype and none the PM *2/*2 diplotype, in people from Central Italy the prevalence of the *2/*2 and *1/*2 was 4.69% and 29.7%, respectively. A significant percentage, though smaller than in central Italy, of IM and PM was observed in Northern Italy as well (1.62 and 23.2%).

### 5.4.3 Potential DGIs involving CYP2C19 gene variants

Genetic variations of CYP2C19 are associated with an altered response to drugs of major clinical relevance, some of which very frequently prescribed in the elderly. CPIC issued specific CYP2C19 pharmacogenomic-guided personalized therapy guidelines for PPIs (Lima et al., 2021), clopidogrel (Scott et al., 2013), Selective Serotonin Reuptake Inhibitors (SSRI) (Hicks et al., 2015) and voriconazole (Moriyama et al., 2018).

PPIs are among the most frequently used drugs in older adults and their prescription in these patients is often inappropriate and involved in DDIs (Hamzat et al., 2012; Pasina et al., 2011; Voukelatou et al., 2019). CYP2C19 PMs and IMs have higher plasma concentrations and respond better to first-generation PPIs (Omeprazole, Lansoprazole, and Pantoprazole) than EMs and UMs. Therefore, the CPIC guideline (Lima et al., 2021) suggests that the initial dose of these PPIs should be increased by 100% in UMs, whereas a 50% dose decrease should be considered for chronic therapy in IMs and PMs. The relevance of these recommendations in the elderly, in which the main issue is the toxicity and not the efficacy of the therapy, remains uncertain.

Clopidogrel is an antiplatelet drug frequently used alone or in combination with acetylsalicylic acid for secondary cardiovascular prevention, and it is largely used in geriatric patients. CYP2C19 is the major CYP responsible for the conversion of clopidogrel, which is a prodrug, into its 5-thiol-metabolite, which blocks $P2Y_{12}$ receptors and, consequently, platelet aggregation. CYP2C19 IMs or PMs are expected to respond to this drug less well than EM and UMs. Considering that even a partial loss of the antiplatelet activity might increase the risk of major cardiovascular events, CPIC recommended not to use clopidogrel in both PMs and IMs whereas this drug should be used at standard dosing in both EMs and UMs (Scott et al., 2013). Regulatory agencies do not require CYP2C19 genotyping before starting clopidogrel therapy and consider this procedure only as "*actionable*". However, the GIANT (Genotyping Infarct Patients to Adjust and Normalize Thienopyridine treatment) study investigators recently showed that the prognosis of CYP2C19 PM or IM undergoing percutaneous stent placement after STEMI could be significantly improved if clopidogrel is given at a double dose or is replaced with prasugrel . Such an approach requires routine preemptive CYP2C19 genotyping on saliva samples. These data are a strong

argument to support the routine use of CYP2C19 genotyping at least in patients undergoing stent placement (Hulot et al., 2020).

SSRIs are a family of antidepressant drugs frequently, though very often inappropriately, used in older adults. Among them citalopram, escitalopram and sertraline are those more extensively metabolized by CYP2C19. It is therefore expected that CYP2C19 UMs will degrade these drugs much more than normal metabolizers, with a consequent reduction in therapy efficacy; on the contrary, plasma concentrations of these SSRIs will be higher than normal in PMs, who will be, consequently, at risk of toxicity. To minimize these risks, the CPIC guidelines suggest that citalopram and escitalopram should not be used in CYP2C19 UMs whereas, in the case of sertraline, the patient should be rapidly switched to a non CYP2C19 metabolized antidepressant if symptoms do not improve; conversely, in PMs the initial dose should be reduced by 50% for all the mentioned drugs (Hicks et al., 2015). None of these recommendations has been enforced by regulatory agencies since the FDA considers CYP2C19 genotyping as *actionable* for escitalopram and citalopram whereas EMA issued no specific recommendation; likewise, no indication on CYP2C19 genotyping has been issued by any of the major regulatory agencies for sertraline.

Voriconazole is a triazole antifungal agent whose major role in therapy is for the treatment and prophylaxis of infections in patients with malignancies and that is only rarely used in non-oncological geriatric patients. CYP2C19 is the main voriconazole metabolizing enzyme and the main issues with the genetic variants of this cytochrome are the loss of efficacy in CYP2C19 UMs and drug toxicity, mainly hepatotoxicity, visual disturbances, and neuropsychiatric symptoms in PMs. The CPIC guideline suggest therefore to select other member of the triazole family both in CYP2C19 UMs and PMs.

Not only CYP2C19 variations may affect the metabolism of drugs frequently prescribed in older adults, but they could also be responsible for DGIs that could potentially increase patient risk for DDIs. As for others CYPs, in the presence of an IM or of a PM phenotype, CYP2C19 inhibitors (also including those which are of weak or intermediate potency) are expected to further decrease an already less than normal enzyme activity and enhance the risk of toxicity when the patients are given CYP2C19 substrates. By cross checking the lists of CYP2C19 inhibitors (Table 2) and of the drugs frequently prescribed in geriatric patients at FOUND (Table 3), we identified, as potential culprits of such DGIs in this patient population, some PPIs (especially esomeprazole and pantoprazole) and SSRIs (citalopram, fluoxetine and fluvoxamine). Based on the prevalence data of CYP2C19 genotypes reported in the previous section, about 20-30 % of the geriatric patient population in Southern Italy could be at risk for these DGIs.

## 5.5 Drug-gene interactions involving CYP2D6

CYP2D6 is a 497 amino acid protein encoded by a small gene of ~4.3 Kbps located in the long arm of chromosome 22 (22q13.2), which consists of nine exons with an open reading frame of 1491 base pairs (Taylor et al. 2020). Its gene locus contains two additional nonfunctional genes, the CYP2D7 and CYP2D8 pseudogenes (Taylor et al. 2020). CYP2D6 is mainly expressed in the liver and, to a much lower extent, in the gut, whereas its expression is negligible in other tissues

(https://www.proteinatlas.org/ENSG00000100197-CYP2D6/tissue). Although CYP2D6 represents only 2-4% of all hepatic CYPs, this cytochrome, which is considered essentially non-inducible, metabolizes about 20% of all approved drugs including highly prescribed cardiovascular and neuropsychiatric drugs (Taylor et al. 2020; Zanger and Schwab, 20013). Since the first studies in the 70s on the metabolism of its substrate debrisoquine, it was realized that CYP2D6 activity is highly variable in the general population, with up to 60-fold differences among individuals. CYP2D6 is indeed, classified as a VIP (*very important pharmacogene*) by *PharmGKB* (https://www.pharmgkb.org/vip/PA166170264).

### 5.5.1. Main CYP2D6 haplotypes and diplotypes and their prevalence in Europe

At the time of writing, 145-star alleles had been uploaded in *PharmVar* (https://www.pharmvar.org/gene/CYP2D6), many of which showing multiple suballeles. In addition, there are also variants not included in any of the star alleles of the *PharmVar* classifications. The majority of CYP2D6 variants are SNVs. A limited number of variants with gene deletions or duplications have also been identified. CYP2D6 variants can be classified according to the change in enzyme activity that they cause. The majority of variations have either no effect or cause a complete or partial loss of CYP2D6 activity; only few variants cause an increase in CYP2D6 activity, and they are all either gene duplications or multiplications. CPIC classifies CYP2D6*1 and CYP2D6*2 as normal variants, CYP2D6*3, CYP2D6*4, CYP2D6*5 and CYP2D6*6, as loss of activity variants (*null alleles*), and CYP2D6*9, CYP2D6*10, CYP2D6*17, CYP2D6*29 and CYP2D6*41 as intermediate activity variants (Table 7).

**Table 7.** Functional classification of CYP2D6 alleles

| Functional class | Main alleles |
|---|---|
| Null alleles | *3, *4, *5, *6, *7, *8, *11, *12, *13, *14, *15, *16, *18, *19, *20, *21, *38, *40, *42, *44, *56 and *62 |
| Alleles with Partial or Residual Function | *10, *14, *17, *18, *36, *41, *47, *49, *50, *51, *54, *55 and *57 |
| Alleles with increased activity | *1x2, *1x ≥3, *2x2, *2x ≥3 |

Different mechanisms are responsible for the complete loss of activity in null alleles including frameshift mutations (as in *3, *19 and *20), mutations disrupting splice acceptor or donor sites (*4 and *11), premature stop of gene transcription (*56) or missense mutations in critically crucial regions of the protein as in *7, which is associated with a H(His) > P(Pro) change in the heme-binding site, and partial (*13 and *16) or whole gene (*5) deletions (Table 8) (Zhou, 2009a; Zhou, 2009b).

Depending on the various combinations of CYP2D6 alleles, diplotypes specifying for either PM, IM, NM or UM phenotypes may occur. More specifically, according to CPIC (https://cpicpgx.org/; Crews et al., 2020) the most observed diplotype/phenotypes are the following:

a) UM: *1/*1xN, *1/*2xN, *2/*2xN
b) NM: *1/*1, *1/*2, *1/*41, *1/*9, *2x2/*10, *10/*41x3
c) IM: *1/*5, *4/*10, *4/*41, *10/*10, *10/*41, *41/*41
d) PM: *3/*4, *4/*4, *5/*5, *5/*6

In the European population, the most prevalent loss of function allele is CYP2D6*4 (18.5%) followed by *5 (2.95%), *3 (1.59%) and *6 (1.11%) (https://www.pharmgkb.org/). The *41 is the most prevalent intermediate activity isoform (9.4%), followed by *10 (1.57%), *9 (2.76%) and *17 (0.39%). At the genotype level, the most common diplotypes are the heterozygous *1/*2 and *1/*4 with a prevalence of 10.5% and 7.03%, respectively. The reference diplotype *1/*1 ranks only third for prevalence and is found in 3.5% of individuals. The *1/*41, *1/*35, *1/*5 and *1/*9 variants have all a prevalence higher than 1% (respectively, 3.5%, 2.08%, 1.12% and 1.05) whereas all the other diplotypes are found in less than 1% of the European population (https://www.pharmgkb.org/). If we look at the phenotypes, the estimated prevalence in the European population is 51.06% for CYP2D6 NM, 6.04% for IM, 0.01% for PM, 3.55% for UM and 1.33% for U/NM. These figures suggest that CYP2D6 activity is different from “normal” in about 49% of the Europeans (Gaedigk et al., 2017).

### 5.5.2. Main CYP2D6 haplotypes and diplotypes in Italy

Few studies have examined the prevalence of the different CYP2D6 variants in the Italian population. None of the subjects of the *Tuscans in Italy* cohort (https://www.internationalgenome.org/) showed the null CYP2D6*3 allele, whereas the prevalence of the other non-functional alleles was 18.7% for *4 (at the diplotype level: 28.0% homozygous and 4.7% heterozygous) and 1.9% for *6 (at the diplotype level only heterozygous with a prevalence of 3.7%). In the same cohort, the most frequent intermediate function variant, CYP2D6*41 (rs28371725) had a prevalence of 14.5% (at the diplotype level: 27.1% heterozygous and 0.9% homozygous). Scordo et al. (2004) determined the CYP2D6 variants in 260 healthy volunteers, mostly from Sicily, and found that 35% of them had an IM diplotype (with a CYP2D6*1 allele in various combination with either *4, *5 or *6), 3.4% were PM (either*3/*4 or *4/*4 or *4/*5) and 8.5% UM (*1/*2x2). Data form the *Italian Tamoxifen Prevention Trial* (Serrano et al., 2011) showed a prevalence of 1.64% for CYP2D6 UM (either *1/*1xN or *1/*2AxN or *1xN/*2A), 9.34% for IM (either 41*/*41, or *41/*5, or *41/*6B, or *41/*9, or *4A/*41 or *4D/*41) and 4.39% for PM (either *3/*4A, or *3/*5, *4A/*4A, *4A/*7, or *4D/*4A). Similar results were reported by De Luca et al. (2010) who found a prevalence of 41.3% for CYP2D6 IM (either *1 in combination with *3, or *4, or *6 or *41) and of 11% for PM (either *3/*4, or *4/*4, or *4/*5). In a series of 174 Italian subjects, Carano et al. (2017) found a prevalence of about 15% for both the loss of function *4 allele and the intermediate activity allele *41. Remarkably, in the same study marked differences were observed in allele prevalence in different Italian

macrozones. Specifically, *4 prevalence was approximately twofold higher in Northern Italy (21.88%) as compared with Central (10.00%) and Southern Italy (11.82%). The non-functional CYP2D6*3 allele was found only in people from Northern Italy, but with a much lower prevalence (0.78%). Two other low-prevalence CYP2D6 non-functional alleles, *5 and *6, showed only little differences in their regional prevalence. The intermediate activity variant *41 was found in 20.91% of the patients from Central Italy, in 18.18% of those from Southern Italy and only in 7.81% of those from Northern Italy. The prevalence of high activity CYP2D6 CNVs *1xN and *2xN was twofold and threefold higher in Southern (1.82% and 2.73%, respectively) than in Northern Italy. In people from Central Italy, only the *1xN variant was detected. At the genotype level, the PM diplotypes CYP2D6*3/*4 and *4/*4 were detected only in people from Northern Italy with prevalence respectively of 1.56% and 7.81% whereas the UM diplotypes were more commonly observed in individuals from Southern Italy (*1/2xN: 3.64% vs 1.56% in Northern Italy and 0 in Central Italy; *1xN/*2: 1.82% vs 0 both in Central and in Southern Italy) with the exception of the *1xN/*1 variant, which was absent in Southern Italy and had a prevalence of 1.56% and 1.82% in Northern and in Central Italy, respectively. The IM diplotypes CYP2D6 *4/*41 and *41/*41 were more frequently observed in Central and Southern Italy than in the other Italian macrozones (*4/*41: 7.27% and 3.64% in Southern and Central Italy vs 3.13% in Northern Italy; *41/*41: 3.64% and 5.45% in Southern and Central Italy vs 0% in Northern Italy).

### 5.5.3. Potential DGIs involving CYP2D6 gene variants

CYP2D16 participates to the metabolism of selected members of many drug families including β-blockers, which are used or the treatment of arterial hypertension, heart failure, arrhythmia, angina pectoris and after myocardial infarction, antidepressants belonging to the families of SSRIs and *Serotonin and Noradrenaline Reuptake Inhibitors* (SNRIs), antipsychotics, such as clozapine and quetiapine, the analgesics codeine and tramadol, and the anticancer drug tamoxifen (Taylor et al., 2020). Some of these drugs are frequently, though sometimes inappropriately, prescribed to geriatric patients and their plasma levels and, consequently safety and efficacy may be affected by CYP2D6 variations. Pharmacogenomic-guided dosing guidelines have been released by major pharmacogenomics associations/societies such as CPIC and the *Dutch Pharmacogenetics Working Group* (DPWG) only for a limited number of these drugs (https://www.pharmgkb.org/guidelineAnnotations). CPIC issued recommendations for atomoxetine (Brown et al., 2019), SSRIs (Hicks et al., 2015), tricyclic antidepressants, opioid analgesics (Crews et al., 2021), the antiemetic drugs Ondansetron and Tropisetron (Bell et al., 2019), and tamoxifen (Goetz et al., 2017).

As already mentioned in the section on CYP2C19, SSRIs are frequently prescribed to older adults even though the Beers criteria discourage their use in the elderly (American Geriatrics Society Beers Criteria® Update Expert Panel 2019). Fluoxetine, fluvoxamine and paroxetine are degraded mainly by CYP2D6, and their dosage should be adjusted according to the CYP2D6 genotype. CPIC suggests that in UMs an alternative SSRI, not degraded CYP2D6 should be used instead of paroxetine

due to the probable lack of efficacy, whereas in PMs paroxetine therapy should be started with initial doses 50% lower than the standard recommended dose (Hicks et al., 2015). No specific recommendation was issued for fluvoxamine prescribing in UMs due to the lack of evidence, whereas a 25-50% reduction of the initial dose was recommended for PMs.

β-blockers are amongst the most frequently used drugs in the elderly with carvedilol, bisoprolol (not a CYP2D6 substrate) and nebivolol ranking among the first 30 prescribed drugs in older adults at FOUND. CYP2D6 gene variants are expected to affect the clinical response to β-blockers causing poor response in UM and drug toxicity, mainly in the form of severe bradycardia, in PMs and IMs. In a recent metanalysis of the studies published on metoprolol, Meloche et al (2020) showed that bradycardia is fourfold more common in PMs than in patients with other CYP2D6 variants. No specific recommendation was issued by CPIC on pharmacogenomic-guided beta-blockers dose adjustment, whereas DPWG has specific guidelines for metoprolol (https://www.g-standaard.nl/risicoanalyse/B0001556.PDF). Specifically, DPWG recommends that, in UMs, treatment should be targeted at the highest recommended dose and, if necessary, doses may be increased up to 2.5 times the standard dose depending on clinical response; on the contrary, if a gradual decrease in heart rate is desired, metoprolol dose should be increased in very small steps in PMs and IMs to reach a maximal dose not higher than 25% and 50% of the standard dose, respectively.

Codeine and tramadol, two analgesic drugs only rarely prescribed to the geriatric patients of our cohort, are both substrates of CYP2D6, which convert these drugs into their active metabolites, morphine and O-desmethyltramadol (M1), respectively. Therefore, CYP2D6 gene variants causing the partial or total loss of enzyme activity will impair the activation of these two analgesics and induce therapeutic failure, whereas those causing an enhanced enzyme expression/activity will increase drug efficacy and potentially induce toxicity. Consequently, the CPIC dosing guideline recommends avoiding codeine and tramadol both in CYP2D6 UMs and PMs, because of the risks respectively of toxicity and therapeutic failure (Crews et al., 2021).

Besides affecting the response to clinically relevant drugs often prescribed to older adults, poorly functioning CYP2D6 variants may also participate to DGIs with CYP2D6 inhibitors, which further decrease CYP2D6 activity and its ability to degrade potentially toxic drugs. By cross-matching the lists of CYP2D6 inhibitors (Table 2) with that of frequently prescribed drugs in geriatric patients at FOUND, we identified the following drugs as potential culprits of such DGIs in older adults in Southern Italy: the strong CYP2D6 inhibitors fluoxetine, paroxetine, fluvoxamine, metoprolol, and the weak inhibitors amiodarone, amlodipine, citalopram, escitalopram, lansoprazole, omeprazole, ranolazine, sertraline, verapamil. As mentioned above, CYP2D6 is considered non-inducible and, consequently DGIs between genes conferring an UM phenotype and drug inducers are not expected to occur.

## 5.6 Drug-gene interactions involving SLCO1B1

The organic anion transporting polypeptide 1B1 (OATP1B1) is a membrane transporter expressed only in the basolateral membrane of liver cells (König et al., 2000). According to the classification of membrane transporters by the HUGO Gene Nomenclature Committee, OATP1B1 is now designated

SLCO1B1. SLCO1B1 transports in a $Na^+$-independent manner a heterogeneous group of organic anion substrates including metabolites such as bilirubin, xenobiotics and drugs from the blood into the hepatocytes (Niemi et al., 2011). More than 60 different drugs are transported by SLCO1B1 with very low specificity and, therefore, many DDIs, some of which clinically relevant, may occur by competition of different substrates at the level of this transporter (Shitara, 2011). SLCO1B1 is a 691 amino acid protein consisting of 12 predicted transmembrane domains and a large extracellular loop which is encoded by a 109 kb gene located on the short arm of chromosome 12 (12p12.2) and consisting of 15 exons (one non-coding) and 14 introns (Niemi et al., 2011). The SLCO1B1 gene is highly variable, and this gene variability corresponds to a significant variability in transporter function in the general population. Therefore, also considering the major role of this transporter in pharmacokinetics SLCO1B1 is listed among the VIPs by *PharmGKB* (Oshiro et al., 2010; https://www.pharmgkb.org/vips).

### 5.6.1 Main SLCO1B1 alleles-and diplotypes and their prevalence in Europe

At the time of writing, 47 SLCO1B1 alleles are listed in the *PharmVar* database, some of which with multiple suballeles. The SLCO1B1*1a suballele represents the “normal” allele and the *1b and *37 suballeles encode for normal function transporters as well. Conversely, the *5, *15, *17 alleles are loss of function variants, which all include the minor allele C at rs4149056 T/C (c.521T>C, p.Val174Ala). The intronic polymorphisms rs4363657 (g.T89595C, intron 11) is in nearly complete linkage disequilibrium with rs4149056, and they are frequently assessed together in pharmacogenomic analyses. The *2, *3, *6, *9, *10, *23, *31 alleles are probably decreased function variants though some controversy still exists, whereas the alleles *14, and *20, both including rs2306283 (Asn130Asp/N130D, A388G/388A>G), have been linked to increased activity of the transporter. The functional effect of the remaining alleles remains to be established. According to *PharmGKB*, more than 40% and 25% of the SLCO1B1 alleles in the European population is represented by the normal function *1 and *37 alleles, respectively, whereas the non-functioning alleles *15 and *5 alleles account for about 17% (15.02 and 2.04, respectively) of total. Since the loss of function haplotypes *5 and *15 and *17 contain all the rs4149056 C variants, SLCO1B1 genotypes are often described according to the rs4149056 variant they contain as TT, TC and CC.

Data from the 1000 Genomes Project Phase 3 (https://www.internationalgenome.org/ ) show that in the European population the minor allele C of rs4149056 has a prevalence of 16% whereas the homozygous CC genotype occurs in 2% of people and the heterozygous CT in 28.2%.

### 5.6.2 Main SLCO1B1 alleles-and diplotypes in Italy

Very few data on SLCO1B1 allele prevalence in Italy are currently available. In the *Tuscans in Italy* cohort of the 1000 genome project (https://www.internationalgenome.org/), the prevalence of the rs4149056 minor allele was 21.5%, and at the diplotype level 3.7% of the subjects were homozygous for the minor allele and 35.5% heterozygous. These data suggest that about 4% of the Italian population SLCO1B1 function could be severely impaired and in more than 35% partially reduced

(https://www.internationalgenome.org/). In the same cohort, the prevalence of the minor allele of rs4363657 was 22.4% with 39.7% of the subjects homozygous and 3.7% heterozygous for this variant. Recently, Licito et al. (2020) reported the results of the SLCO1B1 genotyping in 76 diabetic patients from the Campania Region in Southern Italy: 88.2% of these subjects were homozygous for the minor variant and 18.4% were heterozygous. The reason for such a high prevalence of the minor allele forms in this population remains to be verified in larger studies on healthy people.

### 5.6.3 Potential DGIs involving SLCO1B1 gene variants

SLCO1B1 transports drugs of major clinical relevance in geriatrics including, among the others, statins (mainly simvastatin, pitavastatin, pravastatin and rosuvastatin), ezetimibe, some antihypertensive drugs (enalapril, olmesartan and valsartan), some antidiabetic drugs (empagliflozin and repaglinide), some immunosuppressant drugs (cyclosporine and mycophenolate mofetil), liothyronine and digoxin. SLCO1B1 genetic variants may cause relevant changes in the pharmacokinetics of the aforementioned drugs, sometimes with important clinical implications.

Of special clinical relevance is the potential effect of the SLCO1B1 genotype on the safety of statins, a class of drugs prescribed to almost all older adults. In fact, a strong association between poorly functioning variants of this transporter and an increased risk of myopathy, the most serious ADR caused by these drugs, was described in 2008 already (SEARCH Collaborative Group, 2008) and confirmed thereafter in several larger scale studies (de Keyser et al., 2014; Donnelly et al., 2011). Importantly, not all statins are equally affected by SLCO1B1 genetic variation, with simvastatin and atorvastatin being those more frequently affected (Ahangari et al., 2020). Accordingly, Swissmedic recommends genetic testing for simvastatin and the simvastatin/ezetimibe fix combination whereas FDA considers "*actionable"* the genetic testing for simvastatin, rosuvastatin and pitavastatin (https://www.pharmgkb.org/gene/PA134865839/labelAnnotation). EMA has only drug label informative annotations for statins, with the exception of simvastatin 80 mg, for which genetic testing is recommended (when available) before starting treatment. CPIC issued guideline recommendations for pharmacogenomic-guided statin dose adjustment in 2012, and a revised version in 2014 (Ramsey et al, 2014). The CPIC guidelines focus on simvastatin, for which the evidence is stronger, and recommend not to use this statin or to use doses lower than standard dose in patients with intermediate or low function SLCO1B1 variants. DPWG released guidelines for simvastatin (https://www.g-standaard.nl/risicoanalyse/B0004055.PDF) and for atorvastatin (https://www.g-standaard.nl/risicoanalyse/B0004058.PDF) which recommend not to use either of these statins neither in patients homozygous or heterozygous for the minor rs4149056 allele and suggests using fluvastatin in its place. The French *National Network of Pharmacogenetics* (RNPGx) recommends that SLCO1B1 genetic testing should be performed in patients at risk for myopathy, and that both in homozygous and in homozygous for the minor rs4149056 allele simvastatin should not be given at doses higher than 20 mg, or it should be replaced by another statin, preferentially fluvastatin. While the efficacy of large-scale PKG testing on myopathy occurrence remains to be assessed, recently Vassy et al. (2020) reported

evidence that adopting routine PGx testing does not reduce patient adherence or statin prescribing by medical doctors.

Not only poorly SLCO1B1functioning genetic variants may increase the toxicity of drugs carried by this transporter but they can also enhance the effects of its drug inhibitors and increase the risk of DDIs occurring at its level. Among the drugs prescribed to older adults at FOUND those that could most likely establish such a kind of DGIs are atorvastatin, digoxin, levothyroxine, pantoprazole, rosuvastatin, valsartan and verapamil.

## 5.7 Currently available CDSS with pharmacogenomic integration

The data reported in the previous sections show that genetic variants in key pharmacogenes may modify the susceptibility to inducers or inhibitors of enzymes, pumps and transporters involved in the PK of major drug classes and potentially enhance the risk of clinically relevant DDIs. This suggests that patient's pharmacogenomic profile should be taken into account in medicine review and in CDSS used in its support since it could influence drug safety and efficacy. We interrogated the web and the current scientific literature to search whether tools having these characteristics are already available. Table 8 reports the main pharmacogenomics-based CDSS that we identified in our search. None of the CDSSs identified has been designed for the potential implementation of the IDMP codes that are currently under development.

Most of the currently available PGx-based CDSS have been developed by University Hospitals for internal use upon integration with their local EHRs. These systems have been usually designed as stand-alone tools to suggest dose adjustments or changes of therapy in patients with specific gene variants (e.g., for thiopurines and thiopurine-methyltransferases), and not as more complex systems that incorporate PGx analysis into a larger analysis of DGI, DDIs and DDGIs. For instance, a CDSS, fully integrated with EHR and the pharmacogenomics laboratory, has been developed at the Clinical Pharmacogenomics Service of the Boston Children's Hospital (https://www.childrenshospital.org/centers-and-services/programs/a-_-e/clinical-pharmacogenomics-service-program#). This system generates alerts whenever haplotypes that could be "dangerous" for the prescription of thiopurines, warfarin or abacavir are detected; there is no mention of DGIs or DGGIs (Manzi et al., 2017). Likewise, the Center for Personalized Therapeutics, University of Chicago developed The *Genomic Prescribing System* (GPS) (https://cpt.uchicago.edu/gps/), a web-based portal that reports each of the drugs taken by the patient using a traffic light color code depending on its safety/efficacy based on PGx results. PGx testing results are shown not as raw data but in the form of a succinct, electronic clinical consult with prescribing recommendations and suggestions for drug replacements, if necessary. A prototype CDSS embedded with the EHR was developed at the University of Washington, Seattle to provide PGx-related alerts in the fields of oncology and cardiology (Overby et al., 2015). Other examples of PGx-based prototypes for internal use at local institutions are the CLIPMERGE PGx Program of the Icahn School of Medicine at Mount Sinai, New York, USA (Gottesman et al., 2013), the Personalized Medicine Program of the University of Florida and Shands Hospital (Hicks

et al., 2016; Hoffman et al., 2016;Teng et al., 2014), the Personalized Medication Program of the Cleveland Clinic (Hicks et al., 2016), PG4KDS of the St. Jude Children's Research Hospital in Memphis (Bell et al., 2014; Gammal et al., 2016; Hoffman et al., 2014), the PREDICT software of the Vanderbilt University School of Medicine, Nashville (Peterson et al., 2013; Pulley et al., 2012) and FARMAPRICE, a prototype PGx-based CDSS, which is intended for a larger scale implementation but it is currently tested at the Italian *Centro di Riferimento Oncologico* -Aviano Hospital mainly for oncological patients (Roncato et al., 2019). (Table 8).

Besides these local PGx-based CDSS, a few systems, either commercial or freely available, have been developed to be used at a larger scale in everyday clinical practice. Some of these PGx-based tools are fully developed CDSS which also analyze DDIs and DDGIs.

The medication safety code initiative (https://safety-code.org/) is a system developed at the University of Vienna and freely available upon request that generates a patient-specific QR code based on the results of the PGx analysis of key pharmacogenes: upon scanning this QR code, a specific software generates a PGx passport, i.e., a list of dosing recommendations for major drugs in clinics. Once again, DGIs are not explicitly evaluated by the system. The safety code QR is printed on a plastic card, which is given to patients and should be used whenever a new drug is prescribed. This Safety-Code card has been chosen as a tool to support multilingual PGx-CDSSs by the *Ubiquitous Pharmacogenomics* (UPGx) Project, a Horizon 2020 EU research program, which is testing the potential benefits of large-scale preempting PGx in 7 European countries (Blagec et al., 2018; van der Wouden et al., 2017). Remarkably, in the context of the activities of the UPGx project, a PGx knowledge database was developed to support the implementation of PGx-based recommendations in the various EHR-interfaced CDSSs already available at the sites taking part to the project.

GeneSight (https://genesight.com/) is a paid, commercial service for patients taking psychotropic drugs, which provides PGx testing on patient mouth swabs and generates patient-specific reports which include not only the raw results of PGx testing but also drug prescription advices specifying which drug should be used and which not and whether dose correction is needed.

The YouScript Precision Prescribing Software (https://youscript.com/what-we-do/clinical-decision-support-software/) is a fully developed, commercially available platform that incorporate testing for DDIs, DGIs and DDGIs. It includes data on more than 4000 drugs also including interactions with herbal remedies and OTC drugs. YouScript is fully compatible with EHRs, and a mobile device version is also available. YouScript is now part of the Invitae company, which also provides reagents and services for PGx testing (https://www.invitae.com/en).

GenXys (https://www.genxys.com/) is a software solution package for precision medicine, which includes two software tools: the *TreatGx* software, a CDSS for Pharmacogenetic Testing Interpretation and Precision Prescribing through the assessment of potential DGIs, DDIs and DDGIs, and the *ReviewGx* (https://www.genxys.com/content/mtm-software/), a computer engine for PGx-based automated medicine review. GenXys can be easily integrated with into EHRs, EMRs, and Pharmacy Management Systems (PMS).

In conclusion, several PGx-based CDSS are already available but none of them has been specifically designed for older adults and/or uses IDMP codes for rapid and effective drug identification at the time of medicine review.

**Table 8.** Main PGx-based CDSS (modified from Blagec et al. (2018), Hinderer et al. (2017), and Roosan et al. (2020)).

| Name of the system or of the institution/project | CDSS/project web site | Main features | DDGI | IDMP coding | References |
|---|---|---|---|---|---|
| Clinical Pharmacogenomic Service/ Boston Children's Hospital | na | A software solution developed for internal use at the Boston Children's Hospital Clinical; fully integrated with the EHR it generates alerts based on PGx-testing results upon drug prescribing. | NO | NO | Manzi et al., 2017 |
| University of Washington, Seattle | na | A prototype developed at the University of Washington, Seatlle to incorporate into the PowerChart®/Cerner Millennium® environment, a semi-active PGx-based CDSS which upon prescription of selected drugs triggers either an alert for ordering PGx testing, or, when PGx data are already available, or displays a link to e-resources to provide information to support clinical decision. | NO | NO | Devine et al., 2014<br>Nishimura et al., 2015<br>Nishimura et al., 2016<br>Overby et al., 2012<br>Overby et al., 2015 |
| RIGHT/Mayo Clinic | https://www.mayo.edu/research/clinical-trials/cls-20316196 | A CDSS developed at Mayo Clinic for internal use as a tool of the *Right Drug, Right Dose, Right Time* project on preemptive PGx testing in precision medicine. The system generates PGx alerts at the time of drug prescription by interacting with a EHR in which data on preemptive genotyping of 85 pharmacogenes are stored | NO | NO | Bielinski et al., 2014;<br>Caraballo et al., 2017<br>Ji et al., 2016 |
| PREDICT/Vanderbilt University Medical Center | https://www.vumc.org/predict-pdx/welcome | A locally developed EHR supporting the request for PGx testing either preempting or upon prescription of specific drugs. The system stores genomic data until drugs that could generate DGIs are prescribed; at that time PGx-related alert, a list of potential DGIs and advice for therapy adjustments are generated. | NO | NO | Pulley et al., 2012<br>Peterson et al., 2013 |
| Personalized Medication Program/University of Florida | na | An EHR modified for the preemptive request of CYP2C19 for patients undergoing cardiovascular procedures at the University of Florida. After storage of | NO | NO | Weitzel et al., 2014 |

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|---|---|---|---|---|---|
| | | patient PGx data the system automatically generate a BPA (best practice advice) whenever a CYP2C19 drug substrate is prescribed. | | | |
| Personalized Medication Program/Cleveland Clinic Health System | na | A PGx software developed at the Cleveland Clinic as a complement of the My Family prescription tool, which reports family health information in the HER; it prompts clinicians to ordering PGx testing when prescribing selected drugs or, if this information is already available, it displays PGx results together with BPAs (best practice advices) for PGx-guided drug prescription | NO | NO | Teng et al., 2014 |
| PG4KDS/St. Jude Children Research Hospital | https://www.stjude.org/treatment/clinical-trials/pg4kds-pharmaceutical-science.html | An automated system developed at the St. Jude Children Research Hospital as part of the PG4KDS project to incorporate into the EHR the results of preemptive testing of 225 pharmacogenes, their clinical interpretetion and, when available, direction on drug prescription and dose adjustments according to CPIC guidelines. | NO | NO | Bell et al., 2014<br>Hoffman et al., 2014<br>Gammal et al., 2016 |
| CLIPMERGE PGx/ The Mount Sinai Hospital | na | A PGx knowledge platform independent from, but fully integrated with the Mount Sinai's Epic HER; it has been developed to generate alerts, and suggest specific corrective actions upon drug prescription based on the drug prescribed and the results of patient genetic testing. | NO | NO | Gottesman et al. 2013 |
| FARMAPRICE/Centro Oncologico di Aviano | na | A prototype PGx-based CDSS to identify potential DGIs and suggest therapy adjustment developed at the Centro Oncologico di Aviano and currently tested mainly on oncological patients. | NO | NO | Roncato et al., 2019 |
| GPS/University of Chicago | https://cpt.uchicago.edu/gps/ | A web-based portal developed by the Center for Personalized Therapeutics of the University of Chicago to support PGx-based drug prescription at the Chicago University Medical Center. | NO | NO | O'Donnell et al., 2012<br>O' Donnell et al., 2014<br>Hussain et al., 2016 |

| | | | | | |
|---|---|---|---|---|---|
| Medication Safety Code (MSC)/University of Vienna | https://safety-code.org/ | A research prototype service available upon request that generates a QR code containing the results of patient genetic testing. This QR code is printed onto a plastic card and after scanning provides web-based patient-specific dosing recommendations. | NO | NO | Minarro-Gimenez et al., 2014<br>Blagec et al., 2016 |
| GIMS<br>(Genetic Information Management Suite/the U-PGx project) | https://upgx.eu/ | A knowledge database developed in the context of the UPGx project to support the implementation of PGx-based drug therapy adjustments in the CDSS already available at the clinical sites participating to the project. | NO | NO | Blagec et al., 2018 |
| GeneSight | https://genesight.com/ | A commercial service that performs genetic testing for patients who have to be given psychotropic drugs and also provides a short report with PGx-oriented recommendations for drug prescription. | NO | NO | Altar et al., 2015 |
| YouScript | https://youscript.com/ | A commercial CDSS software solution for the combined evaluation of DGIs and DDGIs. It covers not only prescription drugs but also herbal remedies and OTC medicine. Full integration with EHR. | YES | NO | Brixner et al., 2016<br>Elliott et al., 2017 |
| GenXys | https://www.genxys.com/content/ | A commercial software suite which also includes a tool for precision prescribing based on PGx testing results (TreatGx) and a software for automated medicine review (ReviewGx) which also includes PGx-based recommendations and advice for drug deprescribing. | YES | NO | Dawes et al., 2016 |

## 6. Conclusions and future perspectives

There is an increasing awareness that–PGx-guided drug selection and dose adjustment could help medical doctors in prescribing safe and effective therapies. It has been estimated, indeed, that virtually all patients bear at least one or two actionable genetic variants in important pharmacogenes (Chanfreau-Coffinier et al., 2019; Van Driest et al., 2014). Not only these variants may significantly affect the PK of drugs that they metabolize or transport, but they can also make the patients more sensitive to the effects of inhibitors or inducers of the enzymes, pumps or transporters they encode. This may be especially relevant in patients at high risk of DDIs such as older adults on polypharmacy. Therefore, we aimed to identify the variants in very important pharmacogenes that more likely could affect drug response and cause DGIs in the geriatric population. Table 9 summarizes the main results that we obtained as it shows the main genes that could be involved, the expected prevalence of their main variants and the main drugs that are expected to establish DGIs with them.

The present study has some intrinsic limitations, the most important of which being that the presented DGIs have been identified on a purely theoretical basis and their clinical impact in real patients remains to be established. Likewise, clinical evidence is still missing that genetic testing does actually reduce the prevalence of ADR even though clinical studies such as the *PREemptive Pharmacogenomic testing for prevention of Adverse drug REactions* (PREPARE) supported by the European Commission's Horizon-2020 program are ongoing and should hopefully give a final answer to this question (van der Wouden et al., 2020; https://upgx.eu/study/). Because of this lack of supporting data, very few genetic testing for germline gene variants are considered mandatory by regulatory agencies and concerns have been raised by the FDA that performing such diagnostic tests could even be dangerous since medical doctors could omit needed medicines in patients with a *theoretical* PGx risk (https://www.fda.gov/inspections-compliance-enforcement-andcriminal-investigations/warning-letters/inova-genomics-laboratory-577422-04042019).

Despite these theoretical concerns and limitations, efforts are ongoing for large scale implementation of PGx in everyday clinical practice. In this perspective, the inclusion of PGx data in medicine revision will be certainly helpful and could be fruitfully supported by CDSS in which PGx data are embedded. We performed a web and literature search to identify currently available PGx-based CDSS. We identified several software solutions, some of which are already commercially available and fully compatible with major EHRs. Based on the information freely available on these systems, none of them is tailored for geriatric polypharmacy or has been designed for future IDMP implementation.

The present study was performed to gather the information critical for the next steps of UNICOM T8.5, whose final aim is to provide a theoretical framework for IDMP implementation for precision medicine. In this perspective, we obtained a list of drugs commonly prescribed to geriatric patients at FOUND and of potential drug-gene interactions involving gene variants highly represented in people from Southern Italy. As described extensively in the previous sections, from a practical point of view, the combination between specific gene variants of metabolizing enzymes, pumps or transporters with drugs which affect the activity of these proteins represents a new kind of “combo” drug interactor, which may act as a

perpetrator in drug/drug-gene interactions and enhance or decrease the plasma level and efficacy of other drugs acting as victims. The identification of the most common victims in such a kind of drug/drug-gene interactions, specifically in geriatric patients, will be the objective of the pilot study whose results will be reported in the next deliverable (D8.10) of WP8. This pilot study will be performed in a real-world scenario by examining the drugs prescribed to older adults referring to the geriatric outpatient clinic of FOUND. We will first identify the patients potentially showing the drug-gene “combo” interactors identified in the present study and, then, we will examine which drugs that could be victims of these combos are actually given to these patients. The final results of the pilot will be a list of drug combinations that should require preliminary genetic testing in order to identify whether or not a specific patient bears the risky gene variants that could establish a dangerous drug-gene combos.

The complexity and volume of the information achievable on DDIs and DDGIs which will retrieved by the present study will require the use of digital tools such as CDSSs. On a wider perspective that goes beyond the time-frame of the UNICOM project, the project results will be important for designing a new CDSS to support drug prescription in geriatrics. They will indicate, indeed, when the system should provide alerts to recommend genetic testing before prescribing risky drug combinations. In addition, the CDSS to be developed should be IDMP-based to simplify the identification of the active principles contained in the prescribed medicines and make it usable in many countries with no limitation imposed by regional changes in medicine commercial names. Based on the results of the web search that we performed for the present report, very few CDSS have implemented pharmacogenomics recommendation so far and none of them has been designed for geriatrics suggesting that developing a new CDSS with these characteristics could greatly facilitate a safer and more effective use of medicines in the geriatric population.

**Table 9.** Potential DGIs in older adults from Southern Italy

| Pharmacogene | Functional consequences of the variants | Average prevalence of variants | Potentially interacting drugs | Expected DGI |
|---|---|---|---|---|
| CYP3A4 | Decreased activity | 6% | amiodarone, diltiazem, verapamil, omeprazole and pantoprazole | Further decrease of enzyme activity |
| CYP2C9 | Decreased activity | 20% | amiodarone, fenofibrate, paroxetine, sertraline | Further decrease of enzyme activity |
| CYP2C19 | Decreased activity | 12.7% | esomeprazole, lansoprazole, pantoprazole, citalopram, fluoxetine and fluvoxamine | Further decrease of enzyme activity |
| CYP2D6 | Decreased activity | 10% | fluoxetine, paroxetine, fluvoxamine, metoprolol, amiodarone, amlodipine, citalopram, escitalopram, lansoprazole, omeprazole, ranolazine, sertraline, verapamil | Further decrease of enzyme activity |
| SLCO1B1 | Decreased activity | 40% (35% IM, 4% PM) | atorvastatin, digoxin, levothyroxine, pantoprazole, rosuvastatin, valsartan and verapamil | Further decrease of transporter activity |

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