Life-time Actionable Pharmacogenetic Drug Use: A Population-based Cohort Study in 86 040 Young People With and Without Mental Disorders in Denmark

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Key words
Pharmacoepidemiology, psychopharmacology, genetics, testing

Received 19.04.2021
Revised 31.08.2021
Accepted 08.09.2021
Online publiziert 09.11.2021

Bibliography
Pharmacopsychiatry 2022; 55: 95–107
DOI 10.1055/a-1655-9500
ISSN 0176-3679
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Supplementary Material is available under https://doi.org/10.1055/a-1655-9500.

ABSTRACT
Objective To describe life-time use of current actionable pharmacogenetic (PGx) somatic and psychotropic drugs according to international PGx consortia in people with and without hospital-diagnosed mental disorders in the Danish population.
Methods Population- and register-based observational drug utilization study in 56 065 individuals with mental disorders, i.e. attention-deficit/hyperactivity disorder, autism, bipolar disorder, depression and schizophrenia, and a random, representative sample of 29 975 individuals of the Danish population, born between 1981 and 2005. Individuals were followed from 1995 or birth until 2016 (for a maximum of 22 years). We report prevalence and incidence rates of PGx drug use by age, sex and mental disorders based on redeemed prescriptions between 1995 and 2016.
Results Of the 69 PGx drugs, prescriptions of 39 drugs had been redeemed by the study population by 35 years of age. The use of at least 1 PGx drug varied between 23.1 % in males without mental disorders and 97.2 % in females with schizophrenia. Males with ADHD or autism were the youngest first-time PGx drug users at a mean of 11.6 years. The mean number of different PGx drugs used was 1.2 in males without mental disorders and 5.6 in individuals with schizophrenia. The prevalence of different PGx drugs linked to more than one gene was 25.3 % in males without mental disorders to 94.1 % in females with schizophrenia.
Introduction
Pharmacogenetics (PGx) is the study of the genetic predisposition of individuals, which can result in variability in drug metabolism, pharmacodynamics, or immunogenicity linked to treatment (non-)response or adverse events [1]. PGx aims at optimising treatment outcomes (i.e. increased efficacy or reduced risk of adverse events) by personalising treatment for patients based on their genetic makeup. Actionable PGx drugs are those for which drug or dosing recommendations have been made available by international PGx consortia in evidence-based PGx guidelines [2–4]. PGx guidelines have been provided for a proportionally higher number of psychotropic drugs than other drug classes [5]. Consequently, PGx testing could be of specific benefit for individuals with mental disorders, who often experience adverse events and delayed, insufficient, or non-response to psychopharmacological treatment [6, 7]. Nevertheless, the implementation of PGx testing in psychiatry is lagging behind other specialities such as oncology [5, 8, 9]. The reasons for this have been discussed in recent review articles with a common ground of identified numerous barriers including perceived missing clinical evidence and utility, and knowledge and consensus about PGx testing among psychiatrists [5, 9].

Recently, several observational drug utilization studies of both somatic and psychotropic drugs with actionable PGx implications (PGx drugs) in different populations have contributed to a broader understanding of the potential impact of PGx testing based on the frequency of PGx drug use in larger populations [10–15]. The findings of these studies indicate, for example, that 50% of people using prescription drugs received one or more actionable PGx drug(s) during a 4-year period, 23% of first-time drug prescriptions included actionable drug-gene interactions (DGIs) and in approximately 25% of prescriptions, dose adjustments were recommended [11–14]. A preponderance of actionable psychotropic PGx drug use and the involvement of cytochrome-P450 (CYP) enzymes 2C19 and 2D6 DGIs were commonly observed [10–15]. Although people with mental disorders have not been the focus of these studies and thus, the incidence and prevalence of PGx drug use in people with mental disorders in comparison with an unselected population have not been investigated in detail yet.

One of the reasons for the low implementation of PGx guided dosing in psychiatry is a lack of consensus and specific advice regarding when to test to obtain the optimum and timely benefits. Several options regarding the timing of PGx testing are available, e.g. i) the currently often used ‘reactive testing’ when a patient experiences drug toxicity or non-response, ii) ‘reactive prospective testing’ by executing a PGx test at the time of prescribing to know the PGx status of the patient prior to the start of treatment, and iii) ‘pre-emptive testing’ by executing a panel-based PGx test at a certain time in a person’s life, to know his or her PGx status prior to all future PGx drug prescriptions [11]. A panel-based PGx test including multiple variants in different genes has advantages over single-gene testing in that PGx guided dosing can be applied to PGx drugs with more than one established associated gene (i.e. actionable DGI), or when multiple PGx drugs are used subsequently with different DGIs or concomitantly resulting in drug-drug-gene interactions (DDGI). In addition, panel-based testing offers combinatorial PGx, in which multiple variants of different genes can be interpreted simultaneously to provide a more accurate personal PGx based dosing advice [16, 17]. While panel-based testing has been advocated more recently [5, 9, 13, 18], guidance on whether to test pre-emptively or at which age first PGx drug use can be expected is still missing, which could be supported by observational studies investigating the exposure of actionable PGx drugs since birth.

Aims of the study
To describe prescription drug use of current actionable somatic and psychotropic PGx drugs according to international PGx consortia in people with and without hospital diagnosed mental disorders in the Danish population. The specific aims were to investigate (1) the (life-time) incidence and prevalence of PGx drug use, (2) age at first PGx drug prescription, (3) the mean number of different PGx drugs per individual considering panel-based PGx testing (versus single-gene) and (4) the frequency of PGx drug use related to different genes regarding combinatorial PGx interpretation.

Materials & Methods
Study design
This was a population- and register-based cohort study of individuals born between 1981 and 2005 investigating prescription drug use of PGx drugs in Denmark between 1995 and 2016. The study used data of the Integrative Psychiatric Research (iPSYCH) consortium, which has established a large, unique Danish psychiatry-focused population-based case-cohort study sample (iPSYCH2012), hereafter referred to as iPSYCH sample [19].

Details on the iPSYCH sample have been described previously [19]. In brief, the iPSYCH sample is nested within the entire Danish population of singleton births born to known mothers between 1981 and 2005 (study base: 1 472 762 individuals), who were alive and resided in Denmark on their first birthday [19]. The iPSYCH sample contains five cohorts of a combined total of 57 377 individuals with at least one diagnosis of one of five selected mental disorders, further referred to as case cohorts, i.e. affective/mood disorder (depression), attention-deficit/hyperactivity disorder (ADHD), autism, bipolar affective disorder (BD) and schizophrenia (SZ), and a representative, randomly selected cohort of the general population of 30 000 individuals corresponding to 2.04% of the study base. The members of the population-based cohort are representative of the entire Danish population born between 1981 and 2006, and are at risk of developing the disorder of interest during follow-up.

Conclusion
PGx drugs are commonly used by younger people, more often by individuals with mental disorders and by females. Panel-based PGx testing could contribute to treatment decisions at a very young age.
Data sources

The iPSYCH sample is linked via the anonymized personal identification number, since birth or immigration, to drug prescription data and clinical and socio-demographic information from several Danish national registers, including i) the Danish Civil Registration System (CPR) including information since 1968 on e.g. birth registration, vital status and citizenship [20]; ii) the Danish National Prescription Registry including information on all prescription drugs dispensed at pharmacies since 1994, including e.g. the anatomical therapeutic chemical (ATC) classification code, date and quantity of dispensed drugs [21]; iii) the Danish National Patient Registry including inpatient care information in Denmark since 1977 and outpatient care information since 1995 [22]; iv) the Danish Psychiatric Central Research Register including e.g. diagnosis at and dates of admission and discharge of patients treated at psychiatric departments in Denmark since 1969 [23]; and v) the Danish Register of Causes of Death including cause-specific mortality statistics, with computerized individual records since 1970 [24].

Study population and study period

An overview of the study design and the included individuals with mental disorders and the population sample is shown in ▶ Fig. 1, panel a. The study period was from January 1st, 1995 until December 31st, 2016. As prescription drug information from birth was not available for individuals born between 1981 and 1994, and to assess life-time exposure to prescription drugs, we created two birth cohorts including birth cohort81 born in 1981–1994 and birth cohort95 born in 1995–2005 (with life-time prescription drug exposure). The follow-up time of the individuals started in 1995 (or at birth after 1995), and ended at the date of emigration, death, or December 31st, 2016, whatever came first (▶ Fig. 1, panel b). Individuals of the population cohort developing mental disorders during follow-up were censored from the population sample at the date of diagnosis. If these individuals had received a diagnosis of one of the included mental disorders before December 31, 2012, they were, by study design, included in the case cohorts. These individuals contributed observation time and drug use in both cohorts prior to their diagnoses but accounted only for a small proportion of the population cohort due to low incidence rates [37]. Thus, in this study, the population-based cohort represents the part of the Danish population without the selected psychiatric disorders diagnosed at psychiatric hospitals.

Pharmacogenetic drugs of interest

The international Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) execute literature reviews on PGx and provide peer-reviewed, evidence-based, updatable and detailed PGx guidelines [2–4]. National Danish PGx guidelines do not exist. CPIC and DPWG recommendations partially overlap with labelling recommendations of drugs, such as pimozide and warfarin regarding PGx testing, but PGx testing, in general, is not routinely/widely integrated in Danish clinical practice. We combined information from both CPIC and DPWG PGx guidelines and identified 69 drugs for which actionable PGx recommendations were provided until February 2020 (i.e. actionable PGx drugs, Supplement Table 1) [25, 26]. The list includes drugs from the following drug classes: anaesthetics, antibiotics, analgesics, anti-cancer drugs, anticoagulants, car-
diovascular drugs, proton-pump inhibitors (PPIs) and psychotropics. Of the 69 PGx drugs, 20 drugs (29%) have more than one actionable DGI, and thus have more than one actionable PGx guideline. Seven drugs have DGIs related to both CYP2C19 and CYP2D6, three drugs to TPMT and NUDT15, seven drugs to RYR1 and CACNA1S, one drug to HLA-A and HLA-B, one drug to CYP2C9 and HLA-B and one drug to VKORC1, CYP2C9 and CYP4F2 (Supplement Table 1). We identified the use of actionable PGx using their ATC classification codes from the Danish National Prescription Registry (Supplement Table 1). The retrieved data thus describes drug prescriptions redeemed by the patients at community pharmacies, but the terms 'drug use' and 'drug users' are applied as well in this study.

Data accessibility
The IPSYCH study was approved by the Danish Scientific Ethics Committee (EC: 1-10-72-287-12), the Danish National Board of Health (Sundhedsdatastyrelsen, SDS, FSEID 1999) and the Danish Data Protection Agency (Journal number 2015-57-0002, 62908, umbrella permission Aarhus University). All data is stored at Statistics Denmark and was available in an anonymous form, by remote online access, with special permission in compliance with the Danish Data Privacy Act.

Statistical analyses
We have presented measures of drug use e.g. incidence rates and prevalence, means, standard deviations, separately for two birth cohorts, males and females, and mental disorders case cohorts and the population cohort. We divided the number of users with at least one prescription of a respective PGx drug by the number of total underlying person-years (PY) during follow-up (incidence rates) and by the number of total underlying individuals at the beginning of follow-up (prevalence). The mean age of first-time PGx drug use and the mean number of prescribed different PGx drugs were tested with a t-test to examine whether the mean differences between males and females were statistically significant. A p-value < 0.05 was considered statistically significant. We used SAS ® Lexis macro to calculate incidence rates [27]. Individuals with mental disorders might have received a first actionable psychotropic PGx drug prescription prior to their diagnosis of mental disorders, hence, we have reported descriptive statistics for those individuals who used PGx drugs prior to their first psychiatric hospital diagnosis within each cohort. The number of different DGIs per individual was calculated as the sum of all unique DGIs during follow-up. Concomitant drug use was considered if two or more different drugs had at least one day of overlap of their drug prescriptions. To assess if panel-based testing is more favourable than single-gene testing, we identified the number of prescribed PGx drugs which have more than one actionable DGI, and the total number of users for those drugs.

Due to a restriction from Statistics Denmark and the General Data Protection Regulations, data can only be reported if the number of individuals contributing to aggregated measures exceeds four, which can result in the grouping of data. For sub-analyses to avoid too few counts in individual categories, we grouped mental disorders into mental disorders (A) including predominantly childhood onset disorders and (B) including predominantly adult-onset disorders. All data were processed and analysed using SAS statistical software version 9.4 (SAS Institute Inc, Cary, NC USA) and proportions were compared using MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium).

Results
Table 1 shows the characteristics for both the randomly selected population cohort (N = 29975) and the combined mental disorders case cohorts (N = 56 065) born between 1981–2005 in Denmark, further divided into the two birth cohorts. Males and females were equally distributed in all cohorts, except in the mental disorders case birth cohort 95, which included more males due to a higher prevalence of the young-onset of ADHD and autism in males. Individuals can have a diagnosis of more than one mental disorder and can therefore contribute to several mental disorder case cohorts. During the total follow up of 1 664 266 PY (average of 19.3 years), 115 individuals (0.13 %) died and 3260 individuals (3.8 %) emigrated (0.19 and 6.1 % in the population cohort, and 0.10 and 2.6 % in the mental disorders cohorts, respectively).

Incidence rates of pharmacogenetic drug use
Of the 69 drugs with actionable PGx recommendations, we identified 45 PGx drugs for which prescriptions were redeemed at community pharmacies, 10 of which were used by less than five users each, but were included in further analyses of cumulative or combined use (Table 2). In the population cohort, the highest incidence rates of PGx drug use per 10 000 PY were recorded for oestrogens (429 in females), the analgesics codeine (27 in males and 55 in females) and tramadol (34 in males and 45 in females), followed by PPIs (lansoprazole, omeprazole and pantoprazole) and the antidepressant citalopram (Table 2). In the mental disorders case cohorts, the incidence rates of any of the PGx drugs use per 10 000 PY were higher compared with the population cohort, in particular, psychotropic drugs matching their main indications, e.g. atomoxetine (160 in males and 188 in females) in ADHD, citalopram (248 in males and 306 in females) in depression, aripiprazole (229 in males and 316 in females) in SZ, and lamotrigine (211 in males and 330 in females) in BD. Individuals in the mental disorders case cohorts were prescribed at least one psychotropic PGx drug before their first mental disorders diagnosis with proportions of 50.4 % (ADHD), 38.2 % (autism), 86.9 % (SZ), 86.1 % (BD), and 83.3 % (depression).

Prevalence of pharmacogenetic drug use
In the population birth cohort 81, besides oestrogens used by 80.7 % of females, tramadol (11.7 %), codeine (11.3 %) and lansoprazole (7.7 %) were the most frequently prescribed PGx drugs. In the younger population birth cohort 95, the most used PGx drugs besides oestrogens were omeprazole (3.1 %), codeine (2.7 %) and pantoprazole (2.4 %) (Supplement Table 2). In general, the prevalence of drug users was higher in both the mental disorders case birth cohorts compared with the population cohorts. In the mental disorders case birth cohort 95, the most prevalent prescribed PGx drugs were atomoxe-
### Table 1  Characteristics of study sample.

| Age in groups (y) | Population (N = 15 894) | MD case cohorts (N = 37 437) | Birth cohort81 (1981–1994) Total = 53,331 | Birth cohort95 (1995–2005) Total = 32 709 |
|-------------------|-------------------|-------------------------|---------------------------------|---------------------------------|
| N ( %)            | N ( %)            | N ( %)                  | N ( %)                          | N ( %)                          |
| 18-23             | 2636 (16.6)       | 5605 (15.0)             | 8876 (63.0)                      | 9705 (52.1)                     |
| 24-29             | 7349 (46.2)       | 17 494 (46.7)           | 5205 (37.0)                      | 8923 (47.9)                     |
| 30-35             | 5909 (37.2)       | 14 338 (38.3)           | -                               | -                               |

| Sex               | Female            | 7817 (49.2)             | 19 619 (52.4)                    | 6866 (47.9)                     |
|                   | Male              | 8077 (50.8)             | 17 818 (47.6)                    | 13 657 (73.3)                   |

| Ethnicity‡        | Africa            | 65 (0.4) *              | 73 (0.2)                        | 218 (1.5) *                     |
|                   | Asia              | 176 (1.1) *             | 146 (0.4)                       | 206 (1.5) *                     |
|                   | Australia/Greenland/N. & S. America/Unknown | 16 (0.1) * | 16 (0.0) | 14 (0.1) |
|                   | Denmark           | 13861 (87.2) *          | 33 001 (88.2)                   | 11 294 (80.2) *                 |
|                   | Europe            | 308 (1.9) *             | 403 (1.1)                       | 14 (0.1)                        |
|                   | Middle East       | 145 (0.9) *             | 161 (0.4)                       | 339 (2.4) *                     |
|                   | Mixed             | 1298 (8.2) *            | 3601 (9.6)                      | 1609 (11.4)                     |
| Scandinavia       | 25 (0.2) *        | 36 (0.1)                | 41 (0.3)                        | 26 (0.1)                        |

| Region in Denmark | Capital Region    | 4629 (29.1)             | 10 925 (29.2)                   | 4609 (32.7)                     |
|                   | Middle Jutland    | 3580 (22.5)             | 8764 (23.4)                     | 2991 (21.2)                     |
|                   | North Jutland     | 2178 (13.7)             | 4626 (12.4)                     | 1863 (13.2)                     |
|                   | Southern Denmark  | 1804 (11.4)             | 3180 (8.5)                      | 1453 (10.3)                     |
|                   | Zealand           | 3703 (23.3)             | 9942 (26.6)                     | 3165 (22.5)                     |

| Diagnosis with MD§| ADHD              | 271 (1.7)               | 9402 (25.1)                     | 292 (2.1)                      |
|                   | Affective disorders | 558 (3.5)              | 23 840 (63.7)                   | 72 (0.5)                       |
|                   | Bipolar disorder  | 50 (0.3)                | 2014 (5.4)                      | <5 (0.0)                       |
|                   | Depression        | 516 (3.2)               | 22 025 (58.8)                   | 67 (0.5)                       |
|                   | Autism            | 134 (0.8)               | 6548 (17.5)                     | 223 (1.6)                      |
|                   | Schizophrenia     | 140 (0.9)               | 4271 (11.4)                     | 8 (0.1)                        |

† Birth cohort81 includes individuals born in 1981-1994 and birth cohort95 includes individuals born in 1995-2005; ‡ Ethnicity defined based on parental place of birth as described by Pedersen et al.[18] Europe means countries other than Denmark/Scandinavia and Scandinavia means only Norway, Sweden, Finland, and Iceland. If one parent was born outside of Denmark, that region was used. If both parents were born outside of Denmark, but in different regions, mixed was used. § Summing the percentages of individual disorders might add up to more than 100%, as individuals can carry multiple diagnoses; * Significant difference at a p-value < 0.05. Presented are the characteristics of individuals in the population cohort and combined MD case cohort assessed in 2016. The data is presented in two separate birth cohorts. Data with a number below 5 is presented as < 5 for privacy safety reasons. Abbreviations: ADHD: attention-deficit/hyperactivity disorder, MD: mental disorders.
> **Table 2** Incidence rates of PGx prescription drug use per 10 000 PY of the iPSYCH sample, by population cohort and individual MD case cohorts and sex.

| Drug name         | Population (N = 29 975) | ADHD (N = 19 705) N/10 000 PY | Autism (N = 16 112) N/10 000 PY | Bipolar disorder (N = 2101) N/10 000 PY | Depression (N = 24110) N/10 000 PY | Schizophrenia (N = 4485) N/10 000 PY | PGx DGI |
|-------------------|--------------------------|-------------------------------|---------------------------------|----------------------------------------|-------------------------------------|--------------------------------------|---------|
|                   | Females                  | Males                         | Females                         | Males                                  | Females                            | Males                               | Males   |
| Allopurinol       | -                        | -                             | -                               | -                                      | 1                                  | 1                                   | 2       |
| Amitriptyline     | P 6                      | 2                             | 11                              | 5                                      | 6                                  | 3                                   | 21      |
| Aripiprazole      | P 1                      | 1                             | 47                              | 31                                     | 56                                 | 38                                  | 143     |
| Atomoxetine       | P 2                      | 4                             | 188                             | 160                                    | 49                                 | 51                                  | 32      |
| Atorvastatin      | P 1                      | 1                             | 1                               | 1                                      | 1                                  | 1                                   | 2       |
| Azathioprine      | 2                        | 2                             | 3                               | 2                                      | 2                                  | 2                                   | 4       |
| Carbamazepine     | P 1                      | 1                             | 5                               | 10                                     | 6                                  | 6                                   | 9       |
| Citalopram        | P 31                     | 14                            | 135                             | 51                                     | 84                                 | 42                                  | 314     |
| Clomipramine      | P -                      | -                             | 2                               | 1                                      | 3                                  | 1                                   | 12      |
| Clonazepam        | -                        | -                             | -                               | -                                      | -                                  | -                                   | -       |
| Codeine           | 55                       | 27                            | 89                              | 38                                     | 48                                 | 24                                  | 125     |
| Doxepin           | P -                      | -                             | -                               | -                                      | -                                  | 1                                   | -       |
| Escitalopram      | P 9                      | 4                             | 46                              | 18                                     | 33                                 | 15                                  | 145     |
| Oestrogens        | 429                      | -                             | 484                             | -                                      | 292                                | -                                    | 735     |
| Flucloxacillin    | 10                       | 10                            | 22                              | 16                                     | 17                                 | 14                                  | 14      |
| Fluoxetine        | P -                      | -                             | 6                               | -                                      | -                                  | 1                                   | 1       |
| Haloperidol       | P -                      | -                             | 2                               | 2                                      | 4                                  | 1                                   | 7       |
| Imipramine        | P 1                      | 1                             | 2                               | 1                                      | 2                                  | 1                                   | 3       |
| Lamotrigine       | P 6                      | 4                             | 65                              | 25                                     | 51                                 | 23                                  | 330     |
| Lansoprazole      | 35                       | 20                            | 84                              | 36                                     | 39                                 | 21                                  | 107     |
| Metoprolol        | 7                        | 2                             | 9                               | 5                                      | 9                                  | 3                                   | 15      |
| Nortriptyline     | P 2                      | 1                             | 8                               | 3                                      | 5                                  | 2                                   | 33      |
| Omeprazole        | 38                       | 20                            | 70                              | 31                                     | 50                                 | 23                                  | 86      |
| Ondansetron       | 4                        | 1                             | 7                               | 1                                      | 3                                  | 2                                   | 13      |
| Oxcarbazepine     | P 2                      | 2                             | 5                               | 6                                      | 11                                 | 8                                   | 6       |
| Pantoprazole      | 35                       | 21                            | 82                              | 39                                     | 45                                 | 24                                  | 108     |
| Paroxetine        | P 3                      | 2                             | 16                              | 6                                      | 11                                 | 6                                   | 26      |
| Pimozide          | P -                      | 1                             | 3                               | 6                                      | 2                                  | 4                                   | 1       |
| Risperidone       | P 2                      | 3                             | 60                              | 63                                     | 73                                 | 69                                  | 111     |

| PGx DGI          | HLA-B, CYP2D6, CYP2C19   | HLA-B, CYP2D6, CYP2C19   | HLA-B, CYP2D6, CYP2C19   | HLA-B, CYP2D6, CYP2C19   | HLA-B, CYP2D6, CYP2C19   | HLA-B, CYP2D6, CYP2C19   | HLA-B, CYP2D6, CYP2C19   |

**Notes:**
- **P** indicates pregnancy
- **DGI** indicates drug-gene interaction

**Abbreviations:**
- ADHD: Attention-Deficit/Hyperactivity Disorder
- Autism: Autism Spectrum Disorder
- Bipolar disorder: Bipolar Disorder
- Depression: Major Depressive Disorder
- Schizophrenia: Schizophrenia
- PGx: Pharmacogenetic
- N: Number of cases
- PY: Person-years
- CYP: Cytochrome P450
- HLA: Human Leukocyte Antigen
- SLCO1B1: Solute Carrier Organic Anion Transporter 1B1
- TPMT: Thiopurine S-methyltransferase
- NUDT15: Nudix hydrolase 15
- F5/FvL: Factor V Leiden
- F5/FvL: Factor V Leiden
- *: Indicates significant gene-drug interaction
- : Indicates possible gene-drug interaction
### Table 2. Continued.

The prevalence of individuals using different PGx drugs of different PGx drugs at any time during the follow-up was 43% in females and 25.3% in males in the population cohort (Table 5). In individuals with mental disorders, these numbers ranged between 39.6% in males with autism and 94.1% in females with SZ. The involved DGI are listed in the legend of Table 5.

Concerning combinatorial PGx, the prevalence of individuals who used concomitantly different PGx drugs affected by different DGI was 24.4% of the individuals without mental disorders, 41.3% of individuals with autism or ADH to 69.2% of individuals with BD, SZ or depression (Table 6). In over 80% of these users, the PGx drugs were linked to two different DGI, in 8.1% to three, and in 1.1% of these users, to four DGI.

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**Table 2.** Pharmacogenetic drug use relevant to panel-based testing and combinatorial PGx.

| Pharmacogenetic Drug | Population (N = 29,975) | Depression (N = 24,110) | Schizophrenia (N = 4,483) |
|----------------------|-------------------------|------------------------|--------------------------|
| Population (N = 14,090 PY) | Males | Females | Males | Females | Males | Females | Males | Females | Males | Females | Males | Females |
| Sertraline | 22 | 12 | 4 | 3 | 6 | 4 | 10 | 2 | 4 | 3 | 2 | 4 |
| Simvastatin | 45 | 27 | 12 | 10 | 6 | 4 | 13 | 7 | 9 | 5 | 4 | 6 |
| Vortifluine | 10 | 5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Valproate | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Warfarin | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Zuclopenthixol | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

**Table 3.** Pharmacogenetic drug use relevant to panel-based testing and combinatorial PGx.

| Pharmacogenetic Drug | Population (N = 29,975) | Depression (N = 24,110) | Schizophrenia (N = 4,483) |
|----------------------|-------------------------|------------------------|--------------------------|
| Population (N = 14,090 PY) | Males | Females | Males | Females | Males | Females | Males | Females | Males | Females | Males | Females |
| Sertraline | 22 | 12 | 4 | 3 | 6 | 4 | 10 | 2 | 4 | 3 | 2 | 4 |
| Simvastatin | 45 | 27 | 12 | 10 | 6 | 4 | 13 | 7 | 9 | 5 | 4 | 6 |
| Vortifluine | 10 | 5 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Valproate | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Warfarin | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Zuclopenthixol | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
Discussion

This is the first population-based PGx drug utilization study in 86 040 young people with and without mental disorders in Denmark describing (life-time) incident use of 39 of the 69 actionable PGx drugs according to international guidelines. We found that, by the age of 35 years, at least one actionable PGx had been used by up to 97 % of individuals with mental disorders, i.e., with SZ, and by 65 % of females and 23 % of males of the population cohort (without mental disorders). In individuals with mental disorders, the most frequent actionable PGx drugs corresponded to their psychiatric indications, i.e., atomoxetine in ADHD, citalopram in depression, aripiprazole in SZ, and lamotrigine in BD, related to DGIs involving CYP2D6, CYP2C19, and HLA-B. Moreover, the high use of oestrogens in oral contraceptives related to Factor V Leiden (FvL), the weak opioid analogues codeine and tramadol, the PPIs lan索prazole, omeprazole, and pantoprazole, and citalopram in both the mental disorders and population cohorts also related to the CYP2D6, CYP2C19, and HLA-B indicate the broad applicability of PGx testing in the general population. The first-time users of PGx drugs were as young as (mean age of) 11 years in males with ADHD. Panel-based testing including at least the most commonly identified DGIs could be applicable for 95 % of females with SZ down to approximately 25 % of males in the general population. Combinatorial PGx testing, considering several different drugs and different DGIs at the same time, could be relevant for up to 70 % of individuals with mental disorders and 24 % of the general population without mental disorders.

Life-time incidence and prevalence of pharmacogenetic drug use

Recently several studies in different settings have investigated the incidence and prevalence of actionable PGx drug use, but they neither addressed life-time use or age at first PGx drug prescription nor were they conducted in unselected case cohorts with mental disorders or population-based, thus comparisons are hampered [7, 11–15, 28–30]. Still, the pattern of prevalence of PGx drug use in our study, e.g., the most frequent use of oestrogens, followed by codeine, tramadol, PPIs and citalopram, is similar to the patterns reported by a previous study in Denmark based on publicly available prescription sales data of the general population by age 44 years in 2017 [14]. In comparison with studies in other populations, our observations are in line with findings from the US, UK and the Netherlands applying similar actionable PGx drug criteria. In the US, Samwald et al. found in individuals below 40 years that weak opioids, PPIs, SSRIs, atomoxetine and selected antipsychotics were among the top 8 of incident PGx drugs [11]. In UK, Youssef et al. investigated sales data of overall prescriptions dispensed in 2018, where patients by age 39 years most commonly dispensed prescriptions for antidepressants, oral contraceptives, anti-infectives, and PPIs [10]. Of note, we found generally frequent use of oestrogens, i.e. oral contraceptives related to FvL, which is similar to fre-

| Table 3 | Age at first-time PGx drug use and mean number of different PGx drugs of the iPSYCH sample, by birth and population and MD cohorts and sex. |
|---|---|
| **Age at first-time PGx drug use** | **Birth cohort81 (1981–1994)** | **Birth cohort95 (1995–2005)** |
| **Cohort** | **Females (N = 25 726)** | **Males (N = 16 005)** | **Females (N = 6 299)** | **Males (N = 5 949)** |
| Population | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
| ADHD | 17.8 ± 3.5 | 21.6 ± 5.7 | 15.2 ± 3.3 | 12.9 ± 1.2 |
| Autism | 16.1 ± 3.0 | 19.0 ± 4.9 | 13.2 ± 3.6 | 11.6 ± 1.4 |
| Bipolar disorder | 16.2 ± 4.0 | 17.4 ± 5.4 | 13.1 ± 4.3 | 11.6 ± 4.4 |
| Depression | 16.8 ± 2.8 | 19.9 ± 4.2 | 14.7 ± 2.6 | 13.8 ± 3.5 |
| Schizophrenia | 16.9 ± 2.9 | 19.8 ± 4.1 | 14.3 ± 2.9 | 15.0 ± 2.8 |

| **Mean number of different PGx drugs prescribed** | **Birth cohort81 (1981–1994)** | **Birth cohort95 (1995–2005)** |
|---|---|
| **Cohort** | **Females (N = 25 726)** | **Males (N = 16 005)** | **Females (N = 6 299)** | **Males (N = 5 949)** |
| Population | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
| ADHD | 2.0 ± 1.4 | 1.6 ± 1.1 | 1.4 ± 0.8 | 1.2 ± 0.6 |
| Autism | 4.4 ± 2.5 | 2.8 ± 2.0 | 2.1 ± 1.3 | 1.6 ± 1.0 |
| Bipolar disorder | 3.5 ± 2.3 | 2.4 ± 1.6 | 2.0 ± 1.2 | 1.7 ± 1.0 |
| Depression | 5.3 ± 2.6 | 3.6 ± 2.2 | 3.2 ± 1.6 | 2.3 ± 1.3 |
| Schizophrenia | 4.4 ± 2.4 | 3.1 ± 2.0 | 2.6 ± 1.5 | 2.0 ± 1.2 |

† Birth cohort81 includes individuals born between 1981 and 1994, birth cohort95 includes individuals born between 1995 and 2005. ¥ The differences between males and females in all cohorts are statistically significant, except for the birth cohort95 with bipolar disorder or schizophrenia. Mean age of drug users at their first-time PGx drug prescription and the mean of the number of PGx drugs prescribed in the population and for five individual MD diagnoses are presented. The table is split based on birth cohorts, as we do not have life-time drug use available for individuals in birth cohort81. Individuals who were not prescribed any PGx drug prior to death or data capping are not included in this table. Abbreviations: MD: mental disorders; ADHD: attention-deficit/hyperactivity disorder; iPSYCH: Integrative Psychiatric Research (iPSYCH) consortium, SD: standard deviation.
### Table 4
Prevalence of individuals of the iPSYCH sample with increasing number of different PGx drugs, by population and MD cohorts and sex.

| No. of different PGx drugs | Population | ADHD | Autism | Bipolar disorder | Depression | Schizophrenia |
|----------------------------|------------|------|--------|------------------|------------|---------------|
|                            | Female     | Male | Female | Male             | Female | Male | Female | Male | Female | Male | Female | Male |
|                            | (N=14683)  | (N=15292) | (N=5289) | (N=14416) | (N=3525) | (N=12587) | (N=1292) | (N=809) | (N=16476) | (N=7634) | (N=2083) | (N=2402) |
| N (%)                      | N (%)      | N (%) | N (%)  | N (%)           | N (%)    | N (%) | N (%)  | N (%) | N (%)  | N (%) | N (%)  | N (%) |
| 0                           | 5088       | (34.6) | 11766  | (76.9)          | 799      | (15.1) | 6317   | (43.8) | 976     | (27.7) | 7079   | (56.2) | 52      | (4.0) |
| 1                           | 5409       | (36.8) | 2374   | (15.5)          | 1029     | (19.5) | 3662   | (25.4) | 854     | (24.2) | 2641   | (21.0) | 76      | (5.9) |
| 2                           | 2263       | (15.4) | 732    | (4.8)           | 822      | (15.5) | 1878   | (13.0) | 586     | (16.7) | 1383   | (11.0) | 125     | (9.7) |
| 3                           | 1002       | (6.8)  | 239    | (1.6)           | 712      | (13.5) | 1097   | (7.6)  | 397     | (11.3) | 732    | (5.8)  | 144     | (11.1) |
| 4                           | 489        | (3.3)  | 114    | (0.7)           | 590      | (11.2) | 539    | (4.1)  | 289     | (8.2)  | 366    | (2.9)  | 210     | (16.3) |
| 5                           | 228        | (1.6)  | 37     | (0.2)           | 448      | (8.5)  | 85     | (2.5)  | 182     | (5.2)  | 192    | (1.5)  | 189     | (14.6) |
| 6                           | 125        | (0.9)  | 19     | (0.1)           | 355      | (6.7)  | 241    | (1.7)  | 102     | (2.9)  | 107    | (0.9)  | 141     | (10.9) |
| 7                           | 45         | (0.3)  | 11     | (0.0)           | 177      | (3.3)  | 118    | (0.8)  | 54      | (1.5)  | 43     | (0.3)  | 116     | (9.0)  |
| 8                           | 17         | (0.1)  | -      | -               | 158      | (3.0)  | 76     | (0.5)  | 34      | (1.0)  | 26     | (0.2)  | 93      | (7.2)  |
| 9                           | 16         | (0.1)  | -      | -               | 77       | (1.5)  | 42     | (0.3)  | 20      | (0.6)  | 12     | (0.1)  | 65      | (5.0)  |
| >9                          | 8          | (0.1)  | -      | -               | 122      | (2.3)  | 34     | (0.2)  | 29      | (0.8)  | 6      | (0.0)  | 81      | (6.3)  |

† This number is grouped with data from >7 different PGx drugs, due to data otherwise being <5. The numbers of individuals who were prescribed different numbers of PGx drugs in the population cohort and for five individual MD case cohorts over a mean follow-up time of 19-21 years is shown. Mean (±SD) follow-up times were 20 years in the male population (±4), 19 years in the male population (±4), male patients with ADHD (±3.7) and patients with autism (±3.8), 20 years in the female population (±4) and female patients with ADHD (±3.5) and 21 years in patients with BD (F ±3.6, M ±3.4), depression (F ±3.1, M ±3) and SZ (F ±3, M ±3.1). Abbreviations: MD: mental disorders; ADHD: attention-deficit/hyperactivity disorder; iPSYCH: Integrative Psychiatric Research, PGx: pharmacogenetics, SD: standard deviation; F: females; M: males.

### Table 5
Number of individuals using PGx drugs and the relation with different genes of the iPSYCH sample, by populations and MD cohorts and sex.

| No. of different types of genes | Population | ADHD | Autism | Bipolar disorder | Depression | Schizophrenia |
|---------------------------------|------------|------|--------|------------------|------------|---------------|
|                                 | Female     | Male | Female | Male             | Female | Male | Female | Male | Female | Male | Female | Male |
|                                 | (N=9602)   | (N=3526) | (N=4490) | (N=8099) | (N=5289) | (N=14416) | (N=3525) | (N=809) | (N=16476) | (N=7634) | (N=2083) | (N=2402) |
| N (%)                           | N (%)      | N (%)  | N (%)  | N (%)           | N (%)    | N (%) | N (%)  | N (%) | N (%)  | N (%) | N (%)  | N (%) |
| 1                               | 5473       | (57.0) | 2635   | (74.7)          | 1113     | (24.8) | 4720   | (58.3) | 960     | (27.7) | 3238   | (60.4) | 83      | (6.7) |
| 2                               | 2703       | (28.3) | 765    | (21.7)          | 1237     | (27.6) | 2682   | (33.1) | 821     | (32.2) | 1768   | (32.1) | 207     | (16.7) |
| 3                               | 1237       | (12.9) | 98     | (2.8)           | 1538     | (34.3) | 536    | (6.6)  | 544     | (21.3) | 334    | (6.1)  | 404     | (32.6) |
| 4                               | 142        | (1.5)  | 21     | (0.6)           | 532      | (12.1) | 145    | (1.8)  | 185     | (7.3)  | 78†    | (1.4)  | 493     | (39.8) |
| 5                               | 47†        | (0.5)  | 7      | (0.2)           | 58       | (1.3)  | 16†    | (0.2)  | 39      | (1.3)  | 8†     | (0.1)  | 291     | (1.8)  |
| ≥6                              | -          | -     | -      | -               | -        | -     | -      | -     | -      | -     | -      | -     |

† This number is grouped with data from the immediate cell below, due to data otherwise being <5. The numbers of individuals are shown for different numbers of genes involved in the prescribed PGx drugs in the population and for five individual MD case cohorts over a mean follow-up time of 20-22 years. Mean (±SD) follow-up times were 20 years in the population (±4), 19 years in the male population (±4), 19 years in the female population (±4) and female patients with ADHD (±3.5) and 21 years in patients with BD (F ±2.5, M ±2.4) and female patients with depression (±2.2), and 22 years in male patients with depression (±4.1) and patients with SZ (F ±2, M ±1.7). Percentages are calculated only among PGx drugs users. Genes linked to drug use per cohort: Population (CYP2C19, CYP2D6, CYP4F2, F5/FvL, HLA-A, HLA-B, NUDT15, SLCO1B1, TPMT, VKORC1): Autism (CYP2C19, CYP2D6, CYP4F2, F5/FvL, HLA-A, HLA-B, NUDT15, SLCO1B1, TPMT, VKORC1, CYP3A5); ADHD (CYP2C19, CYP2D6, CYP4F2, F5/FvL, HLA-A, HLA-B, NUDT15, SLCO1B1, TPMT, VKORC1); Schizophrenia (CYP2C19, CYP2D6, CYP4F2, F5/FvL, HLA-A, HLA-B, NUDT15, SLCO1B1, TPMT, VKORC1). Abbreviations: MD: mental disorders; ADHD: attention-deficit/hyperactivity disorder; iPSYCH: Integrative Psychiatric Research, PGx: pharmacogenetics, SD: standard deviation; F: females; M: males.
We found that the mean age of the earliest PGx drug use in the cohort born between 1985–2006 was 11 years in females and 13 years in males. The mean age of PGx drug use for all individuals without mental disorders was 13 years in males and 15 years in females. Pre-emptive PGx testing was performed in 22% of males and 52% of females. We further estimate that premature PGx testing in females was performed by the age of 35 years in individuals with mental disorders.

Considering any other study assessing the time incident use of PGx drugs, we are not aware of data indicating that the frequency of PGx testing in females aged 35 years was lower than in the population without mental disorders. However, considering that most females aged 35 years are users of oral contraceptives, there is a potential for bias in the data. Further studies are needed to determine the appropriate age for PGx testing in females aged 35 years.

We also found that the frequency of PGx testing in females aged 35 years was lower than in the population without mental disorders. This is mainly due to the fact that PGx drugs are mainly used in females aged 35 years and the frequency of PGx testing in females aged 35 years is lower than in the population without mental disorders. However, considering that most females aged 35 years are users of oral contraceptives, there is a potential for bias in the data. Further studies are needed to determine the appropriate age for PGx testing in females aged 35 years.

Additional risk factors for thrombosis such as smoking, diabetes, and obesity were considered in our study. However, the number of women with these conditions was too small to make meaningful comparisons. Furthermore, the prevalence of these conditions may differ across different populations, and future studies are needed to determine the appropriate age for PGx testing in females aged 35 years.
tial of pre-emptive testing, but not based on life-time use, in different patient populations across disorders, age ranges, settings and study set-ups (e.g. follow-up times) leading to a wider range of 11.2% to 97% of individuals exposed to one or more PGx drugs over a 2–20 year follow-up period, thus are not directly comparable with our findings [11, 28, 36–38].

Panel-based and combinatorial pharmacogenetic testing

Our results indicate, as discussed earlier, the utility of panel-based testing due to the frequent use of several PGx drugs related to different DGIs. Panel-based testing in particular, of a core panel including variants of CYP2D6 and CYP2C19 has been endorsed by many PGx societies and implementation initiatives [14, 15, 30, 39]. These efforts are now being further supported by a recent meta-analysis finding that plasma levels of various antidepressant and antipsychotic drugs are associated with CYP2D6/CYP2C19 genotype-predicted metabolizer status supporting genotype-based dosing recommendations and ultimately PGx testing in people with mental disorders initiating psychotropic treatment [40].

An additional benefit of panel-based PGx testing is the opportunity to execute combinatorial PGx, which considers the effect of multiple variants in different genes for PGx-based dose adjustments. This is of importance when a single drug has multiple actionable DGIs or when multiple PGx drugs are used concomitantly. The substantial number (a third) of individuals affected by multiple DGIs and 24.4% (population) to 69.2% (BD, SZ, depression cohorts) using multiple PGx drugs concomitantly in our study indicates the potential benefit from combinatorial PGx. Multiple PGx drugs acting on the same enzyme affected by genetic variation leading to DDGs and related PGx guided drug dosage recommendations are yet not provided in international public guidelines and rarely transparently in commercial combinatorial PGx tests but are under development [41–43]. In addition, the difference between the number of individuals using a drug and the number of individuals who require necessary action vary from <1% to 50% with divergent geno-phenotypes [14], which is largely dependent on the combination of actionable PGx guidelines for geno- or phenotypes and frequencies of these geno- and phenotypes.

Strengths and limitations

The strengths of the current study are that it presents data of a large population-based case-cohort of individuals with mental disorders and a population cohort representative for the entire Danish population of young age. The study has no bias in the selection of individuals, very little missing data and little loss to follow-up due to the registry-based study set-up using the Danish Civil Registration System. All these strengths allow a valid estimation of first-time as well as life-time PGx drug use in Denmark, and these estimates are likely to extrapolate to countries with similar drug utilization patterns and health care systems. This study has some limitations. First, a considerable number of individuals have no drug data registered from birth until 1995 solely affecting birth cohort81. By dividing the cohort into two birth cohorts, we were able to present PGx drug use from birth up to the end of the study for the remaining individuals born since 1995 (ages 11–21). This affects the interpretation of the age of first PGx drug use and the mean number of PGx drug use. We lack data of the youngest years of individuals in birth cohort81, with a maximum of the first 11 years of an individual born in 1984. This might result in a higher mean age for birth cohorts81 due to the left-truncation. We have data until a maximum age of 11 years for individuals born in 2005, thus individuals starting a first PGx drug at age 12 or older are not included in the calculations. This might result in a lower mean age for birth cohorts95 due to right-truncation. Yet, since we know the average age of onset of disease, we expect that the real answer, e.g., ADHD and autism lies close to the mean age identified in birth cohorts95, compared to the other disorders with a real age of first PGx drug use in between the results for birth cohorts 1 and 2 [39, 40, 44, 45]. Another limitation is that hospital-based data is missing from the drug registries, excluding some actionable PGx drugs such as anti-infectives and drugs used in anaesthesia. Moreover, we present a drug utilization study of current actionable PGx drugs. The results presented in this study might be affected in the future by changing trends in drug use or updated PGx guidelines, for example including new PGx drugs. Lastly, the iPSYCH population is rather homogeneous with 88% of Danish or European ancestry, 10% mixed ancestry, and only up to 2% of Non-European ancestry, partially due to the design of the study including individuals born in Denmark since 1981. Among the commonly used PGx drugs identified in the current study, this may affect estimates for the even greater utility of PGx testing of drugs affected by CYP2C19 variations or HLA-B variants, both of which are more frequent in individuals with Asian ancestry; or CYP2C9 variations in individuals with African ancestry and should be considered in PGx adjusted dosing recommendations of relevant drugs [46, 47].

In conclusion, PGx drugs are commonly used by young individuals, with more frequent PGx drug use among young individuals with mental disorders and females. PGx testing could be beneficial already at a very young age (adolescent). Panel-based PGx testing would be preferable over single-gene testing, based on the number of individuals using PGx drugs subsequently or concomitantly and the number of different drug-gene interactions involved.

Data Availability Statement

The data that support the findings of this study are available from Statistics Denmark. Restrictions apply to the availability of these data, which were used under license for this study. Data are available in an anonymous form, by remote online access with the permission of Statistics Denmark, the National Centre for Register-based Research (NCRR) and the Centre for Integrated Register-Based Research at Aarhus University (CIRRAU).

Funding

The study was funded by unrestricted grants received by C. Gasse of the Alfred Benzon Foundation, Denmark, and NovoNordisk Foundation (NNF17OC0029488) and by C. Lunenburg of the Lundbeck Foundation, Denmark (R322-2019-2404). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
Conflict of Interest

The authors declare no conflict of interest.

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