Pharmacogenomics and Personalized Medicine

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ORIGINAL RESEARCH

Individualized Drugs' Selection by Evaluation of Drug Properties, Pharmacogenomics and Clinical Parameters: Performance of a Bioinformatic Tool Compared to a Clinically Established Counselling Process

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Purpose: Inefficacy and safety concerns are main medications' problems, especially in the case of poly-therapies, when drug–drug interactions may alter the expected drug disposition. Ongoing efforts are aimed to establish drug selection processes aimed to preemptive evaluation of a plethora of factors affecting patient's specific drug response, including pharmacogenomic markers, in order to minimize prescription of improper medications. In previous years, we established at the University Hospital Sant'Andrea of Rome, Italy, a Precision Medicine Service based on a multi-disciplinary experts' team. The team is in charge to produce a drug therapy counselling report, including pharmacogenomic, pharmacokinetic and pharmacodynamic considerations. In this study, we aimed to evaluate the performance of this established "manual" process of therapy selection with a novel bioinformatic tool, the Drug-PIN system.

Patients and Methods: A total of 200 patients diagnosed with Major Depressive Disorders or a depressive episode in Bipolar Disorder, with at least three previous failed treatments, who underwent pharmacogenomic profiling and therapy counselling in the Sant'Andrea Hospital from 2017 to 2020. The baseline poly-therapy of these patients was re-evaluated and optimized by Drug-PIN. Results of the Drug-PIN poly-therapy evaluation/optimization were compared with the results of the original poly-therapy evaluation/optimization by therapy counselling. To compare the results between the two processes, the risk associated with each poly-therapy was classified as low, moderate, or high.

Results: The number of baseline poly-therapies classified in low-, moderate- or high-risk did not change significantly between manual system or Drug-PIN system. As the counselling process, also the Drug-PIN system produces a significant decrease in the predicted treatment-associated risk.

Conclusion: Drug-PIN substantially replicates the output of the counselling process, allowing a substantial reduction in the time needed for therapy evaluation. Availability of an effective bioinformatic tool for proper drug selection is expected to exponentially increase the actuation of targeted therapy strategies.

Keywords: poly-therapy, pharmacogenomics, Precision Medicine, Drug-PIN, drug–drug interactions

Received: 20 April 2021
Accepted: 16 June 2021
Published: 5 August 2021

Introduction

The World Health Organization (WHO) recognized improper drug prescription as a main societal challenge and launched, in 2017, the Third WHO Global Patient Safety Challenge: Medication Without Harm,[1] introducing the aim of reducing severe and avoidable drug-related harm by 50% in five years as follows:

> It is set within the philosophy of patient safety previously developed by WHO, namely that errors are inevitable and provoked in large part by weak health systems, and so the challenge is to reduce their frequency and impact.

In the same document, the cost associated with medication errors is estimated at around US $42 billion annually.

Improper prescription has a close relation with the inter-individual biological variability in drug response, which is a multi-factorial phenomenon determined by both static factors as the genomic make-up, and by dynamic factors, as ageing, lifestyle, environment. In addition, the concomitant use of multiple drugs (eg, polypharmacy) presents the peculiar risk of drug–drug interactions (DDIs), which can alter drugs' pharmacokinetics (PKs) or pharmacodynamics (PDs), causing adverse effects and/or inefficacy.[2–5] Moving from these considerations, the Precision Medicine (PM) approach developed thanks to the evolution of biotechnologies and bioinformatics.[6] Pharmacogenomics represented the main boost of PM, allowing to pre-emptively detect genetic variations in drug metabolic enzymes/transporters and drug targets, which in turns affect drug's PKs and PDs leading to inefficacy/toxicity.[7,8] The primary goal of PM is the shift of healthcare systems toward a more preventive approach, through early identification of unique patient's features which are informative about the individual risk of diseases' onset and progression and about the better treatment strategies. The cancer paradigm depicts the success of PM to improve therapy efficacy/safety, allowing drugs' selection according to specific molecular alterations in the tumor tissue, and to mitigate/avoid severe, and potentially lethal, side effects.[9] In other medical fields, the PM approach is less effective, since a standardization process for clinical application has not been clearly stated in accepted guidelines. Indeed, the development of guidelines for oncology has been easier since generally, few molecular markers are clearly associated with the patients' response to a specific drug treatment.[9] But in different clinical settings, the picture is more complex. A relevant example is the psychiatric treatment, which involves a plethora of diseases, often sharing similar symptoms but with different and often not completely understood etiology. Thus, "patient-sized" treatment selection cannot be easily targeted to specific molecular alterations.[10] Moreover, the frequency of poly-therapies in psychiatric diseases increases the frequency of unfavorable DDIs, affecting the rate of efficacy, safety and patient's compliance to the treatment. In such a scenario, which also includes even more fragile patients as the child and the elderly,[10,11] systematic application of pharmacogenomic screening and DDIs analysis could help appropriate drug prescription, but it is hampered by the complexity of interpretation of hundreds of molecular interactions.

In the Sant'Andrea Hospital of Rome we established, by 2005, a Precision Medicine service based on availability of a pharmacogenomics and metabolomics analysis platform and of a multi-disciplinary team composed by molecular biologists, pharmacologist, pharmacogenomics experts and clinicians.[12–16] The main goal of this service is the adequate selection of pharmacological treatments to ensure better clinical outcomes and patient's safety. A bottleneck of the process is the time-consuming consultation of multiple knowledgebases followed by manual annotation to produce a "therapy counselling report", where patient-specific recommendations about the use of specific drugs are listed.

Recently, a Clinical Decision Support Systems (CDSS) for patient-sized drug selection was released, the Drug-PIN system.[17,18] Interestingly, the system embeds information from multiple knowledge bases and sources, including the international commission CPIC (Clinical Pharmacogenetics Implementation Consortium),[19] reporting the functional effect on drug disposition of validated pharmacogenetic markers; the Beers- and PRISCUS-Lists,[20,21] which consider age-related drug problems; the drug-labels themselves, which list clinically relevant DDIs. Further, the CDSS takes into account the effect played on drug action by patient's renal and liver functionality.

Since such automated bioinformatic tools for poly-therapy selection are expected to drastically shorten the timeline to produce a "patient-sized" therapy counselling report, in this study we sought to explore the consistency of individualized drug poly-therapy selection by the Drug-PIN system. Thus, we evaluated the performance of Drug-PIN in comparison with the established, structured but manual methodology actioned by the expert team at the Sant'Andrea Hospital of Rome.

Table 1 Main Patients' Characteristics (N=200). Continuous Variables are Reported as Mean ± Standard Deviation, Categorial Variables are Reported as Absolute Counts

Patient's Characteristics	Value
Age (years)	56.94 ± 12
Gender (F/M)	111/89
BMI (kg/m^2)	24.6 ± 6
No. of prescribed drugs	8 ± 4
No. of smokers, caffeine, alcohol consumers	60, 112, 83
GFR (mL/min)	94 ± 15
ALT, AST (U/l)	23 ± 5, 26 ± 8
No of clinically relevant polymorphisms*	18 ± 6

Notes: *Out of 75 analysed pharmacogenetic markers, heterozygous or homozygous carriers.

Materials and Methods

Study Design and Population

This is a retrospective, comparative study evaluating the concordance of poly-therapy optimization results obtained by a manual or an automated methodology.

The poly-therapies were referred to 200 outpatients (Table 1) at the "Centre of Personalized Medicine" and "Service of Personalized Mental Health and Pharmacogenomics", Sant'Andrea Hospital, Sapienza University, Rome, from 2017 to 2020. Inclusion criteria were: diagnosis of Major Depressive Disorders (MDD) or a depressive episode in Bipolar Disorder (BD) with treatment failure in at least three previous psychopharmacological trials; poly-therapy including at least 4 drugs; availability of a manually compiled "poly-therapy drug counselling" including pharmacogenomic evaluation (see below); informed written consent. Exclusion criteria were: minor of legal age (≤18 years) or advanced age (≥75 years); substance use disorders (except nicotine); neurological (epilepsy, major neurocognitive disorder, Parkinson's disease) or severe acute organic illnesses (major cardiovascular disorders and hypertension, diabetes, malignancy, renal failure).

The study was approved by the Ethics Committee of the University of Rome and registered under Prot. 987/2014.

Manual Poly-Therapy Drug Counselling

All patients were genotyped for 75 polymorphisms in 29 pharmaco-genes including Phase I and Phase II drug metabolizing enzymes, drug transporters and drug targets (Table 2).

Table 2 List of Genes and Polymorphisms Analyzed in the Patients' Cohort

Gene	Polymorphism
ABCB1	rs1128503, rs1045642
ABCC1	rs45511401
ABCC2	rs8187710, rs17222723, rs717620
ABCG2	rs2231142
SLCO1B1	rs4363657, rs4149056
SLC15A2	rs2257212
5-HTT	5HTT-LPR
CYP1A1	rs1048943
CYP1A2	rs2069514, rs762551
CYP2A6	rs28399433, rs1801272
CYP2B6	rs2279343, rs3745274, rs3211371, rs28399499
CYP2C8	rs11572103, rs1058930
CYP2C9	rs1799853, rs1057910
CYP2C19	rs6413438, rs12248560, rs4244285, rs4986893, rs28399504, rs56337013, rs72558186
CYP2D6	rs1065852, rs28371706, rs16947, rs61736512, rs1080985, rs35742686, rs3892097, rs28371725, rs5030655, rs5030867, rs5030656, rs72549351, rs72549354, Gene deletion, Gene duplication
CYP3A4	rs2740574, rs35599367
CYP3A5	rs776746
COMT	rs4680, rs4633, rs4818
EPHX1	rs2234922, rs1051740
NAT1	rs5030839, rs56172717, rs56379106, rs4986782
NAT2	rs1801280, rs1799930, rs1799931
TPMT	rs1800462, rs1800460, rs1142345
UGT1A1	rs8175347
UGT2B17	Gene deletion
DRD2	rs1800497, rs1799732, rs1801028
DRD3	rs6280
HTR2A	rs6314, rs7997012, rs6311
HTR2C	rs6318
OPRM1	rs1799971

The manual poly-therapy drug counselling was carried-out by a multidisciplinary team composed by a psychiatrist, a clinical pathologist and a pharmacogenomics expert. The counselling workflow consisted of a preliminary evaluation of the baseline poly-therapy, performed by the pharmacogenomics expert who reviews the DDIs and the genomic profile of the patients, highlighting dangerous interactions and scoring the poly-therapy associated risk as "low", "moderate" or "high". The risk level is intended to include both safety concerns and inefficacy concerns. Then, the poly-therapy optimization was carried out as follows: ì) the pharmacogenomics expert proposes a list of alternative drugs aimed to minimize interactions; the alternative drugs are scored as "usable", "not recommended" and "unusable"; ìì) the psychiatrist proposes a novel drugs combination discussing the alternative choices with the pharmacogenomics expert and the clinical pathologist, who reviews the biochemical profile of the patients, as liver and renal function, counselling about drug selection and dosage; iv) the optimized therapy is prescribed to the patient by the psychiatrist. The main knowledgebases used for the counselling were: Drug-bank;[22] PharmGKB (based on CPIC guidelines);[23] Transformer;[24] national and international drug agency websites.[25–27]

Drug-PIN Poly-Therapy Optimization

The patient's parameters evaluated by the Drug-PIN CDSS are: age, sex, body mass index, smoking, alcohol and caffeine consumption, diagnosis, creatinine, transaminase level, pharmacogenomic markers; the drug-related parameters evaluated by the Drug-PIN are: drug–drug interactions, official drug labels, disease guidelines.[17,18] The process for automated poly-therapy optimization consists of four steps: ì) loading of all the available patient's parameters, including demographic, phenotypic and genotypic data, on the "patient information" form; ìì) loading the names of the drugs composing the baseline poly-therapy on the "therapy" form; ìì) reviewing eventual medication problems detected by the system; the extent of the medication problem is expressed by a numerical value, the Drug-PIN score, and highlighted by a color code ranging from green (low-risk drug cocktail, score range 0–20) to yellow (moderate risk drug cocktail, score range 21–60) and to red (high-risk drug cocktail, score >60); iv) exchanging drugs in the baseline cocktail choosing among the proposed list of alternative drugs (eg, same therapeutic target). The proposed alternative drugs are ranked according to the extent of improvement in the Drug-PIN score, allowing rapid optimization of the baseline therapy.

Statistics

Data were analyzed using the IBM SPSS statistics software version 25. To compare the results of poly-therapy evaluation/optimization between the manual and Drug-PIN systems, the low-, moderate- and high-risk classification of the manual process were equated to the Drug-PIN scores 0–20 (low-risk), 21–60 (moderate risk) and >60 (high risk). Numerical variables have been analysed using the Student's *t*-test and linear regression analysis, categorial variables were analyzed by Fisher exact test.

Results

The study cohort included 200 subjects (111 females, 89 males) with a mean age of 56.9 ± 12 (Table 1).

The baseline poly-therapies were classified by manual counselling as "moderate risk" or "high risk" in 66% and 34% of the analyzed cohort, respectively. Re-evaluation of the baseline poly-therapy by the Drug-PIN system classified 56% of samples as "moderate risk" and 44% as "high risk" (Figure 1). The discrepancy is due to an increased rate of high-risk classification by the Drug-PIN system compared to the manual system. Conversely, no case of manual high-risk assignment was classified as moderate risk by Drug-PIN. However, Fisher's exact testing shows no statistically significant difference between manual and Drug-PIN classification methods (p=0.192).

Manual optimization allowed to re-design 82% of the baseline poly-therapies improving the supposed safety/efficacy profile, eg, to shift from high or moderate risk to moderate or low risk.

Drug-PIN optimization allowed to shift 70% of the baseline poly-therapies from high or moderate risk to moderate or low risk. However, the 30% of optimized therapies which could not be re-classified in a lower risk category, improved the numerical risk score from a mean value of 47.43 ± 8.96 to a mean value of 30.83 ± 6.63 (the greater the Drug-PIN score, the greater the risk associated with the therapy), a statistically significant change (p=0.0003). Considering the overall sample, the Drug-PIN scores for the baseline poly-therapies and the optimized poly-therapies were 60.23 ± 33.65 and 24.40 ± 19.36, respectively ($p < 0.00001$). Linear regression analysis (Figure 2) shows that the average Drug-PIN score is improved by almost 59% after automated poly-therapy optimization.

Discussion

Improper drug usage represents one of the most burdening medical concerns, causing inefficacy, toxicity and non-

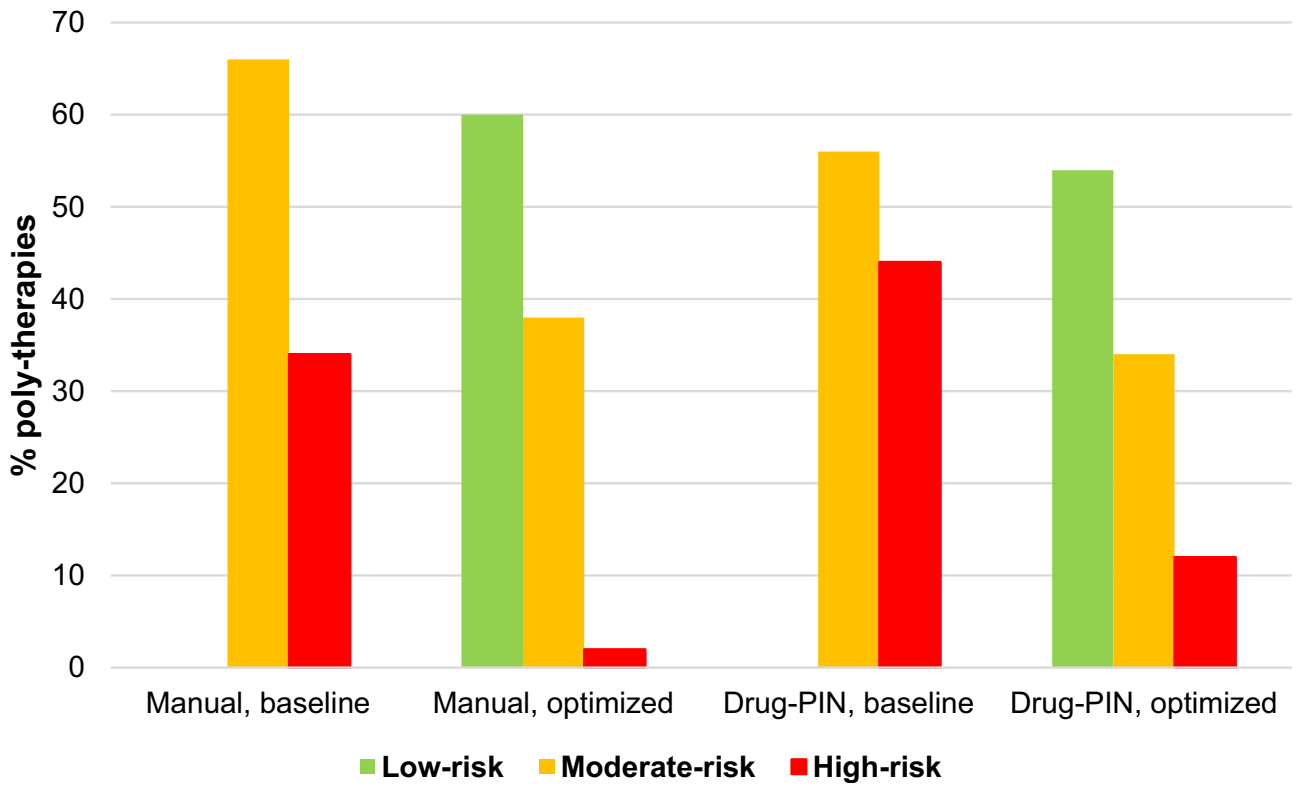

Figure 1 The percent values of baseline/optimized poly-therapy classified as low-, moderate- or high-risk by manual or Drug-PIN processes are shown.

adherence to the medical prescription. Still, deep knowledge is available about the biological determinants of drug's action, theoretically allowing to actuate the so-called Precision Medicine and patient-sized drug selection. However, considering the number of drugs available (about 4000 active ingredients)[24] and the huge number of drug interactions with molecular actors inside the cells (receptors, metabolic enzymes, drug transporters), also determining drug-drug interactions, it is hard to systematize such knowledge in a ready-to-use medical decision support system. With the aim to create a service for Precision Medicine and patient-sized therapy selection, the University Hospital Sant'Andrea of Rome developed, starting from 2005, a molecular diagnostic facility employing a multi-disciplinary team including biologists, pharmacogenomics experts, pharmacologists, and medical specialists. This team established the manual workflow for drugs therapy optimization described in previous and present paper.[12–16] This approach requires consultation of different public knowledge bases reporting drug-drug interactions, drug labels, pharmacogenomic markers,[22–28] annotation of patient's characteristics relevant to drug disposition, and manual compilation of a patient's therapy optimization report. Thus, the main limits inherent to the manual approach are: i) it is time consuming, limiting the number of patients who can access the service; ii) in borderline cases, different operators may misclassify the therapy-associated risk, according to a personal opinion about the "weight" of different variables; iii) the personnel involved in the multidisciplinary team for therapy optimization need intensive training to acquire adequate skills and confidence in the process. Thus, the availability of an automated tool for poly-therapy evaluation/optimization would have a striking effect on the accessibility to Precision Medicine, overcoming the above cited limits of manual therapy counselling. In this paper, we aimed to verify the precondition to the clinical implementation of the recently launched CDSS system, Drug-PIN, which appears to include the full spectra of variables affecting drug response that our multidisciplinary team evaluates manually, that are: pharmacogenomic profile, DDIs, biochemical profile (as renal and kidney function). Drug-PIN re-evaluation of 200 baseline poly-therapies shows that there were no statistically significant differences between the number of baseline poly-therapies classified as moderate- or high-risk between the manual and the automated evaluation process. However, one-by-one comparison of the manual and automated classification system showed that the Drug-PIN system is more severe in risk

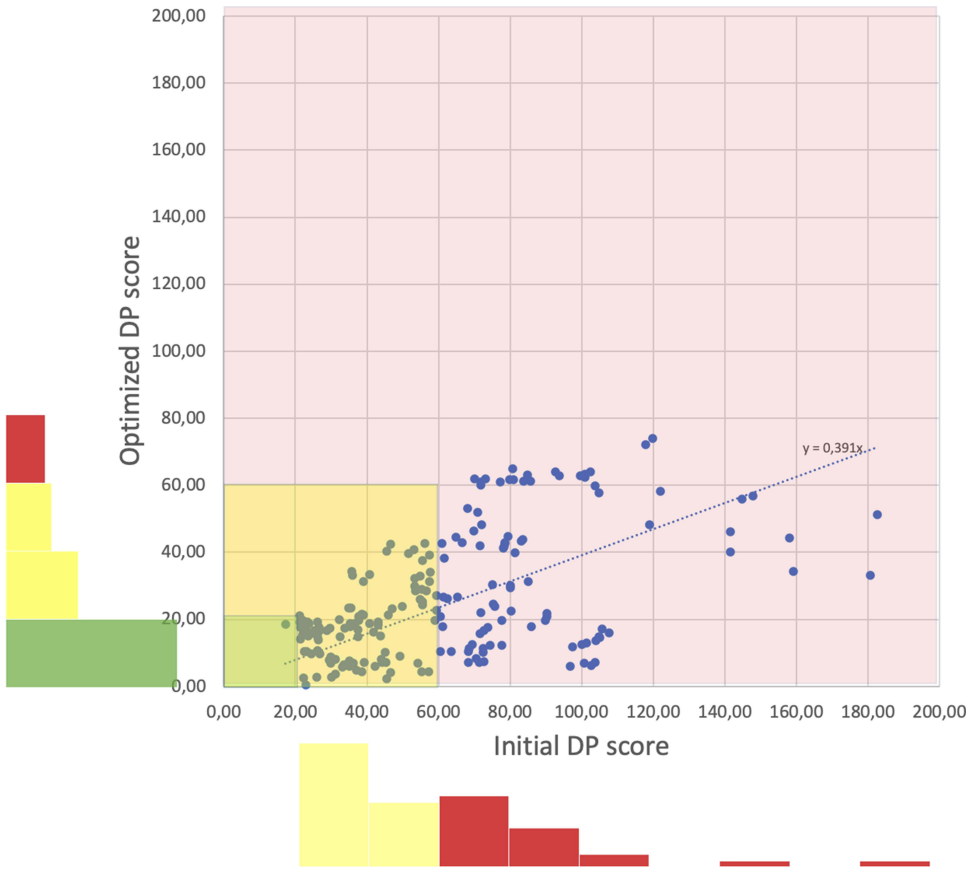

Figure 2 The therapy-associated risk scores calculated by the Drug-PIN system have been plotted for baseline (x-axis) and optimized (y-axis) poly-therapies. The green-yellow-red color code indicates predicted low-, moderate- or high-risk poly-therapy.

classification, since about a 15% of the poly-therapies manually defined at moderate-risk were classified as high-risk by the automated system. This effect could be explained by two main consideration: first, while manual counselling considers the most relevant effects of genotype, phenotype and DDIs, the automated system can evaluate a massive number of information from multiple sources, producing a higher number of warning than the manual evaluation. From a clinical point of view, a more severe classification is satisfactory since guarantees the safety of the patient according to a precaution principle.[13] The higher stringency of the Drug-PIN evaluation process is also evident by a slight decrease (82% vs 70%) in the percent of baseline poly-therapies which could be re-designed as a lower risk class therapy. However, it should be noted that the Drug-PIN system produces a numerical risk score, the higher the value the higher the risk, that is significantly decreased between baseline and optimized poly-therapy even when the categorial (moderate or high) classification does not change. Thus, the therapy optimization diminishes the estimated overall risk, anyway.

Finally, we should consider that the risk associated with a minor fraction of poly-therapies could not be improved at all. In these cases, the evaluation of risk score contributes to improve treatment outcomes allowing adequate patient's monitoring and follow-up.

In summary, the Drug-PIN CDSS showed poly-therapy evaluation/optimization performance conforming to the manual counselling system that we routinely practice in our Precision Medicine facility. The turnaround time of the automated system is strikingly shorter than our manual counselling process. It is hard to estimate a mean turnaround time for the manual poly-therapy counselling, since it is affected by the number of drugs and by the number of variant pharmaco-genes carried by the patients, but ranges between 3 and 6 working hours. Conversely, the turnaround time using the Drug-PIN system is essentially independent from the complexity of the drug-cocktail or the individual genomic profile; the most time-consuming step in the Drug-PIN process is the creation of a patient's phenotype/genotype including all relevant patient data like lab values, etc., but has the advantage to save the data,

saving time in subsequent evaluations, as add-on therapies. The time to results is about 10–15 minutes from baseline poly-therapy evaluation to poly-therapy optimization. Shortening the timeline to the "patient-sized" therapy counselling report by adoption of a CDSS as Drug-PIN, will enable to reach more rapidly the milestones for system-level adoption of Precision Medicine. In particular, the possibility to perform pre-emptive therapy optimization in a significantly increased number of patients, will enable prospective clinical studies, aimed to assess the added value of individualized therapy selection in terms of outcomes, patient compliance and not least, healthcare costs. Indeed, the evaluation of the cost-benefit ratio in definite clinical settings is essential to drive policymakers and health-care stakeholders towards the adoption of innovative processes for proper drug prescription.

Conclusions

To demonstrate the conformity of available bioinformatic tools to previous accepted processes of individualized drug selection and prescription is essential to gain the acceptance level and willing to use among practitioners. The proof of the clinical utility of such CDSS is crucial as well. A preliminary analysis of data (not shown) from an ongoing study evaluating clinical efficacy of Drug-PIN poly-therapy optimization in a therapy-resistant psychiatric patients' cohort (similar to that analyzed in this study) shows a significant improvement of the clinical outcome after prescription of the Drug-PIN optimized therapy. Conclusive results from this study are expected to validate the efficacy and safety of the automated approach to patient-sized ploy-therapy selection.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki, was approved by the Ethics Committee of the University of Rome and registered under Prot. 987/2014. Participants provided their signed written consent.

Patents

IA Number: PCT/IB2019/052310 "System, Method and Software Program for Managing the Interaction between Drugs".

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

Professor Robert Preissner and Professor Maurizio Simmaco are members of the Advisory Board of Drug-PIN AG. The Drug-PIN AG is holder of the patent PCT/IB2019/052310. Professor Antonio Del Casale reports personal fees from Edra, personal fees from Imagine, personal fees from GlaxoSmithKline, personal fees from Fidia, outside the submitted work. Mr Andreas Eckert reports personal fees from Drug-Pin AG, outside the submitted work. The remaining authors declare to have no conflict of interest.

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