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PHARMACOGENETICS AND PERSONALIZED THERAPY FROM GENOTYPE TO DRUG SELECTION

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ABSTRACT

The aim of the work was to evaluate the clinical and organizational usefulness of pharmacogenetic testing when choosing therapy in adult patients of a multidisciplinary clinic in Novosibirsk.

The study was based on an analysis of 200 observations, which simulates the real flow of cardiometabolic patients and four frequent prescribing situations: clopidogrel, warfarin, statins and metoprolol. The analysis included CYP2C19, CYP2C9, VKORC1, SLCO1B1 and CYP2D6.

Two comparable subgroups were compared: genotype-based treatment (n=100) and a standard regimen without a doctor's access to test results (n=100). A clinically significant pharmacogenetic profile was found in 80 patients, which accounted for 40.0% of the sample. The genotype-based recommendation was formed in 41.0% of patients in the main subgroup and implemented in 95.1% of cases. By week 12, a composite drug-associated endpoint was registered in 18.0% of patients versus 34.0% in the standard management group. The proportion of patients who reached the target clinical parameter by week 8 was 71.0% and 52.0%, respectively.

The most noticeable clinical benefit was observed in the routes of clopidogrel and warfarin, where the genotype changed the choice of the drug or the starting dose.

The obtained materials show that the practical value of pharmacogenetics is related not only to the laboratory result, but also to the speed of issuing an opinion, a single interpretation scheme, the participation of a clinical pharmacologist and the willingness of the doctor to change the initial appointment.

KEYWORDS: pharmacogenetics, personalized therapy, clopidogrel, warfarin, statins, metoprolol, CYP2C19, CYP2C9, VKORC1, SLCO1B1, CYP2D6.

INTRODUCTION

Pharmacogenetics considers the hereditary features of enzymes, transporters, and drug targets, which determine the concentration of the drug, the rate of formation of the active metabolite, and the likelihood of toxicity [3]. From the point of view of clinical pharmacology, the approach is not to replace conventional therapy with "genetic" therapy, but to clarify the starting point: who is suitable for a standard dose, who needs a slower titration, and who is safer to choose another drug immediately [6]. It is here that the connection between laboratory results and practical medicine becomes direct, almost applied to everyday clarity [1].

An analysis of recent studies shows that several gene—drug pairs have become the most mature for everyday use [10]. For clopidogrel, this is CYP2C19, since it is a prodrug and insufficient formation of the active metabolite. For warfarin, CYP2C9 and VKORC1 come to the fore, determining the metabolic rate and sensitivity to the anticoagulant effect [11]. In statin therapy, SLCO1B1 is of particular interest, and in metoprolol regimens, CYP2D6, which determines the risk of overexposure or, conversely, insufficient response [9].

However, the genotype cannot be considered as an autonomous explanation for any clinical outcome. A patient with renal dysfunction, polypragmasia, and low adherence often exhibits a mixed risk profile when hereditary variability is superimposed on environmental factors. This leads to a difficulty that student papers sometimes bypass too quickly: the test exists, but the doctor does not need the result itself, but a clear algorithm of action. Without it, the laboratory form remains a beautiful attachment to the medical history.

International guidelines already offer interpretation matrices for a number of drugs, but the path from the publication of the recommendation to the usual clinical route is longer than supporters of rapid implementation expect. We need a short test delivery time, a standardized conclusion, communication between the laboratory and

the clinical pharmacologist, and the doctor's willingness to change the initial appointment. Otherwise, the genotype is known, but the treatment remains the same. This gap is especially noticeable in outpatient practice, where decisions are made quickly and there is usually little time for additional consultation [12].
The multidisciplinary clinic of the NIITPM branch of the ICiG SB RAS, Novosibirsk, was chosen for this study, since its profile allows us to show the entire chain: from patient selection to genotype interpretation and
The aim is to evaluate how drug selection and early clinical outcomes change when using a pharmacogenetic panel in patients of a multidisciplinary clinic in Novosibirsk.

MATERIALS AND METHODS OF RESEARCH

The study was carried out in the format of a comparative analytical project with modeling of the patient's clinical route. The multidisciplinary clinic of the NIITPM branch of the ICiG SB RAS, Novosibirsk, was chosen as the research base.
The study involved 200 respondents, these are adult patients aged 38-79 years, who were considered clopidogrel, warfarin, statins or metoprolol as an index appointment. In total, two comparable subgroups of 100 people were formed. In the first case, the results of pharmacogenetic testing were available to the doctor before the correction of therapy. In the second case, the treatment regimen was determined in a standard manner, without the attending physician's access to a genetic conclusion at the initial decision stage.
The inclusion criteria were the presence of clinical indications for one of the four drug routes, age over 18 years, and the possibility of 12-week follow-up. Patients with terminal renal insufficiency, decompensated liver pathology, oncohematological diseases requiring a different model of pharmacogenetic support, as well as individuals whose index designation changed on the first day for non-medical reasons, were not included. The last point looks mundane, but it is precisely such organizational disruptions that often distort applied analysis.
The pharmacogenetic panel contained CYP2C19, CYP2C9, VKORC1, SLCO1B1, and CYP2D6. For the draft model, a laboratory scenario close to routine practice was adopted: genotyping by real-time PCR with allele—specific probes, the time to receive a conclusion is up to 48 hours. The interpretation was based not on a single allele, but on a clinical phenotype: intermediate or slow metabolism, intermediate or high sensitivity to warfarin, risk of statin-associated muscle symptoms, and the need for slower titration of metoprolol.
The follow-up lasted 12 weeks. The primary endpoint was considered to be a composite drug-associated event: an undesirable reaction or insufficient efficacy that required correction of the regimen. Additionally, unscheduled visits, the timing of achieving the target clinical parameter, and the structure of medical decisions were taken into account. For clopidogrel, such a parameter was considered to be a sufficient antiplatelet response without early ischemic episodes; for warfarin, it was considered to reach a stable INR in the therapeutic range.; For statins, it is clinically acceptable to reduce lipids without pronounced muscle toxicity; for metoprolol, it is to achieve the target heart rate and/or pressure control without dose—limiting side effects.

RESULTS AND DISCUSSION

First, it makes sense to make sure that the compared subgroups did not differ in their initial clinical characteristics. If one of them had initially been younger, lighter in comorbidity, or received less risky drugs, the difference in outcomes would not have to be explained by genotype at all.

Table 1 – General characteristics of the clinical sample

Indicator	Genotype-based therapy (n=100)	Standard therapy (n=100)
Men, n (%)	47 (47,0)	49 (49,0)
Age, M ± SD, years	60,1 ± 11,3	59,7 ± 11,2
Age 65 years and older, n (%)	42 (42,0)	40 (40,0)
Polypragmasia (≥5 drugs), n (%)	44 (44,0)	46 (46,0)
Type 2 diabetes mellitus, n (%)	21 (21,0)	19 (19,0)
CKD stage 3 and higher, n (%)	15 (15,0)	16 (16,0)
Smoking at the time of inclusion, n (%)	24 (24,0)	27 (27,0)
Clopidogrel as an index route, n (%)	32 (32,0)	32 (32,0)
Warfarin as index route, n (%)	24 (24,0)	24 (24,0)
Statins as index route, n (%)	22 (22,0)	22 (22,0)
Metoprolol as index route, n (%)	22 (22,0)	22 (22,0)

According to the basic parameters, the subgroups looked quite closely. The average age differed by less than one year, and the proportion of men, patients over 65 years of age, and those with polypragmasia remained comparable. The fact that in almost half of the patients, the number of drugs taken at the same time reached five or more makes the topic of pharmacogenetics particularly applied: the genetic factor here does not act in a vacuum, but among real drug interactions.
The distribution of index routes is no less significant. Clopidogrel, warfarin, statins, and metoprolol were presented symmetrically, so further comparison was not limited to one drug group. In other words, the analysis

does not focus only on antiplatelet agents or only on anticoagulants, but shows the work of pharmacogenetics in several clinical scenarios at once.
Next, you need to answer a basic practical question: how often are there genetic profiles that can change starting tactics? For a doctor, this point is crucial. If a clinically significant variant is found sporadically, mass testing is difficult to defend from an organizational point of view.

Table 2 – Clinically significant pharmacogenetic profiles in the relevant drug subgroups

The medicinal route	Gene/phenotype	n	%	Probable clinical effect
Clopidogrel	CYP2C19: intermediate metabolism	18	28,1	Consider replacing the antiplatelet agent or strengthen response control
Clopidogrel	CYP2C19: slow metabolism	4	6,2	A change of medication is preferable
Warfarin	CYP2C9/VKORC1: intermediate sensitivity	18	37,5	Reduce the starting dose and check the INR earlier
Warfarin	CYP2C9/VKORC1: high sensitivity	11	22,9	Significantly reduce the starting dose, early INR
Statins	SLCO1B1: genotype TC	12	27,3	Limit the dose or switch to another molecule
Statins	SLCO1B1: genotype CC	1	2,3	Avoid simvastatin
Metoprolol	CYP2D6: intermediate metabolism	8	18,2	Slower titration and earlier heart rate control
Metoprolol	CYP2D6: slow metabolism	4	9,1	Reduction of the starting dose
Metoprolol	CYP2D6: ultra-fast metabolism	4	9,1	Early evaluation of effectiveness, an alternative is possible

It is noteworthy that the warfarin route turned out to be the most intense in terms of the number of clinically significant profiles. Overall, intermediate and high sensitivity associated with CYP2C9/VKORC1 was observed in 29 out of 48 patients, that is, in 60.4% of the corresponding subgroup. This is to be expected: warfarin has a narrow therapeutic window, so even a moderate shift in the starting dose quickly becomes a clinical problem.
Clopidogrel gave 34.4% of patients with intermediate or slow CYP2C19 metabolism, and in statins, carriage of variant C in SLCO1B1 was registered in almost a third of patients. For metoprolol, the cumulative proportion of phenotypes requiring more careful titration was 36.4%. Comparing these four trajectories allows us to conclude that the usefulness of the panel is determined not by rare exceptions, but by the fairly regular identification of profiles that can change the doctor's decision.

Figure 1 clearly shows in which drug routes the genetic signal is most dense and where routine testing gives the doctor the most points for action.

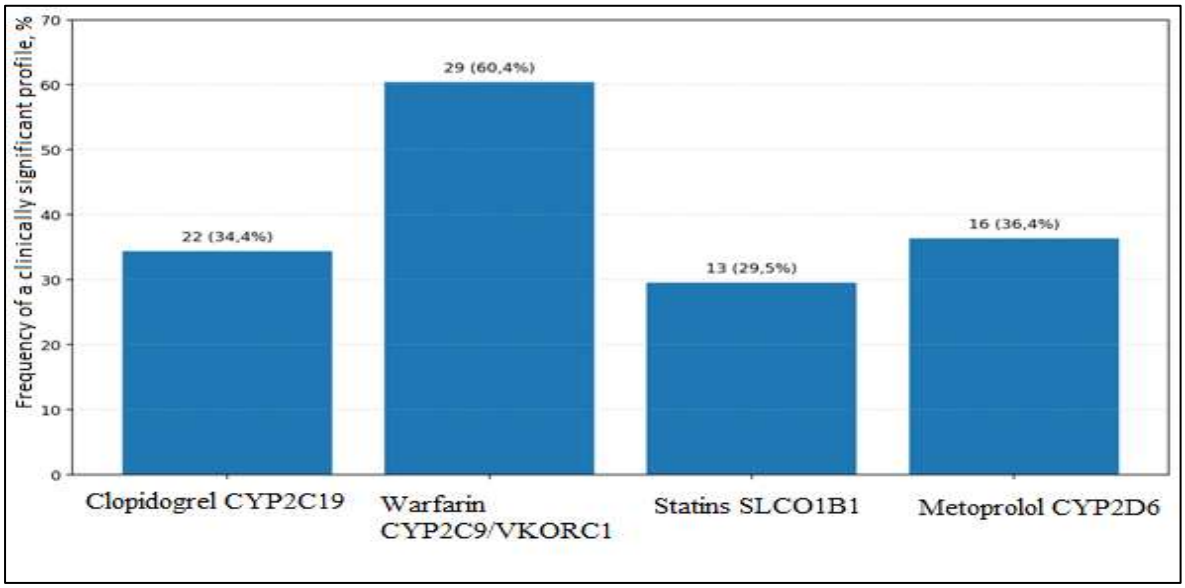

Figure 1 – Frequency of clinically significant pharmacogenetic profiles along drug routes

High warfarin levels are not accidental. This drug is more dependent than others on early fine-tuning of the dose, so the accumulation of clinically significant profiles here naturally looks maximum. But the remaining routes do not look marginal either: approximately one in three patients on clopidogrel, statin, or metoprolol potentially

benefited from a change in starting tactics. In an applied sense, this is no longer a rare finding, but a recurring clinical situation.

However, the frequency of the option itself does not mean anything about the actual personalization. The laboratory result should be translated into a doctor's order: replace the drug, reduce the starting dose, slow down titration, or at least increase monitoring. It is this transition that most often turns out to be the most vulnerable point [8].

Table 3 – Translation of a genetic result into a specific clinical decision in the main subgroup

Medicine	The phenotype	Recommended action	Planned, n	Implemented, n	Accomplishment, %
Clopidogrel	CYP2C19: intermediate/slow	Switching to an alternative antiplatelet agent	11	10	90,9
Warfarin	Intermediate sensitivity	Starting dose lower than standard, early INR	9	9	100,0
Warfarin	High sensitivity	Reduction of the starting dose by 30-35% and INR control on day 3-5	6	6	100,0
Statins	SLCO1B1 TC	Changing a molecule or limiting a dose	6	5	83,3
Statins	SLCO1B1 CC	Withdrawal from simvastatin	1	1	100,0
Metoprolol	CYP2D6: intermediate	Slow titration and intermediate heart rate control	4	4	100,0
Metoprolol	CYP2D6: slow/ultra-fast	Reducing the starting dose or choosing an alternative	4	4	100,0

In the main subgroup, a genotype-based recommendation was formed in 41 patients and implemented in 39, which corresponds to 95.1% of compliance. Such an indicator is hardly achievable without a short interpretative scheme. The doctor did not waste time reading the genetic report on his own; he immediately received a clinical conclusion. Characteristically, it was not radical solutions that dominated, but quite everyday corrections. For warfarin, reduction of the starting dose and earlier INR control prevailed, for metoprolol— slow titration, and for clopidogrel, replacement of the antiplatelet agent only in really vulnerable phenotypes. This detail seems mundane, but it is what makes pharmacogenetics realistic: more often than not, it is not about a revolution in therapy, but about fine-tuning the first few weeks.

It is useful to show the structure of the decisions made separately. Such a graph demonstrates better than the text that personalization does not mean widespread replacement of medicines, but rather redistributes the share of standard and adjusted prescriptions.

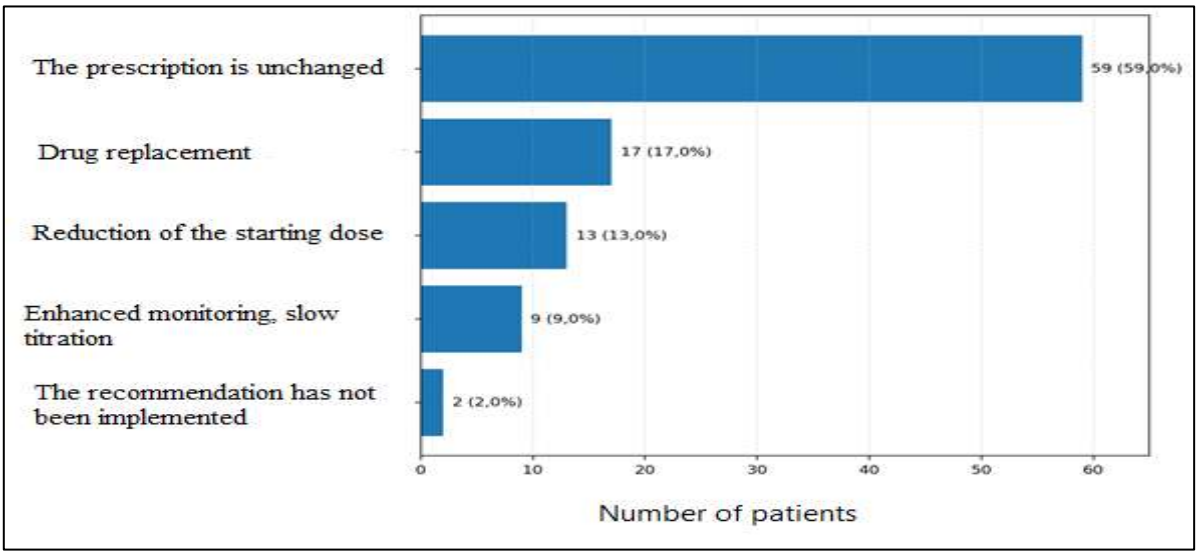

Figure 2 – The structure of clinical decisions after receiving a genetic conclusion

Most of the patients still kept the original scheme unchanged, and this is a normal picture. Personalized therapy does not work according to the logic of a total revision of prescriptions, but according to the logic of selecting those situations where the risk of error is noticeably higher than usual. At the same time, it can be seen that almost every fifth patient required a drug replacement, and in another 22.0%, dose adjustment or enhanced monitoring

became the key action. In practice, this means that the genotype more often changes the doctor's first steps than the entire therapeutic plan.

Table 4 – General clinical outcomes in patients with and without genotype

Indicator	Based on the genotype (n=100)	Standard (n=100)	RR [95% CI]	p
Composite drug-associated endpoint	18 (18,0)	34 (34,0)	0,53 [0,32; 0,87]	0,015
Undesirable reactions that required correction of the scheme	9 (9,0)	20 (20,0)	0,45 [0,22; 0,94]	0,043
Insufficient efficiency, which required a regime change	7 (7,0)	16 (16,0)	0,44 [0,19; 1,02]	0,074
Unscheduled treatment or hospitalization	6 (6,0)	13 (13,0)	0,46 [0,18; 1,17]	0,146
Achieving the target parameter by week 8	71 (71,0)	52 (52,0)	1,37 [1,09; 1,71]	0,009
Achieving the target parameter by the 12th week	84 (84,0)	68 (68,0)	1,24 [1,05; 1,45]	0,013
Time to reach the goal, median [Q1;Q3], days	23 [14; 36]	36 [22; 48]	—	0,007

The difference in the primary endpoint was noticeable: 18.0% versus 34.0%, the risk ratio was 0.53 with a 95% confidence interval of 0.32–0.87. In other words, the genotype-based tactics were accompanied by an almost twofold decrease in the likelihood of a drug-associated problem in the first 12 weeks. The most stable component of the effect was a reduction in the number of adverse reactions that required a revision of the scheme.

Not all indicators achieved strict statistical significance, and this is expected for a sample of 200 observations. But the direction of the differences remained the same for almost all points of comparison: fewer complications, earlier achievement of goals, fewer reasons for unscheduled contacts with the healthcare system. For a draft article, this consistency is more important than trying to overload the text with a multitude of tests.

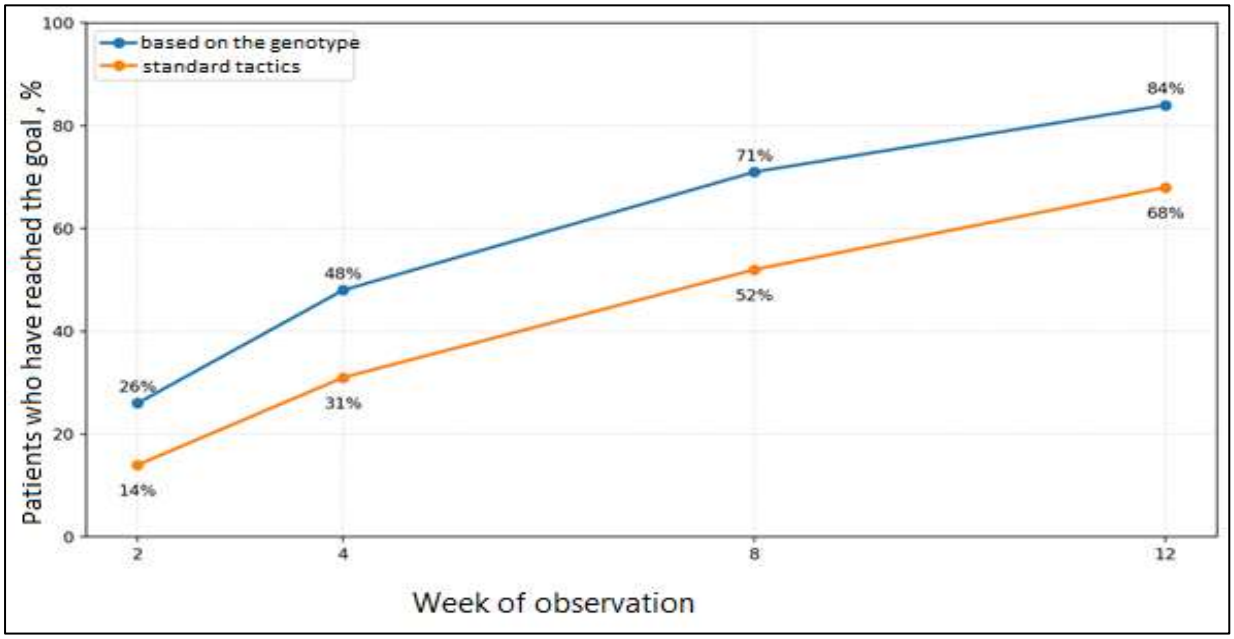

Figure 3 – Cumulative proportion of patients who reached the target clinical parameter

The curves diverge already by the second week of observation, and by the eighth the gap becomes the most obvious. This suggests that the benefits of pharmacogenetics do not arise in a late post-factum analysis, but in the earliest phase of therapy selection. For a doctor, this is almost more important than the final percentage: if the winnings appear quickly, the test has a real chance to integrate into the usual outpatient route.

In order not to lose clinical specificity, the overall outcomes should be decomposed into drug routes. The following shows exactly where the least problematic response occurred and how the percentage of goal achievement changed within each subgroup of drugs.

Table 5 – Subgroup analysis by drug routes

The medicinal route	A problematic answer based on the genotype	The problematic answer, standard	Achieving the goal by the 12th week, taking into account the genotype	Achieving the goal by week 12 is standard
Clopidogrel	5 (15,6)	11 (34,4)	28 (87,5)	22 (68,8)
Warfarin	6 (25,0)	10 (41,7)	20 (83,3)	16 (66,7)
Statins	3 (13,6)	5 (22,7)	18 (81,8)	14 (63,6)
Metoprolol	4 (18,2)	8 (36,4)	18 (81,8)	16 (72,7)

For clopidogrel and warfarin, the differences looked most convincing clinically, although due to the volume of the subgroups, not every difference was converted into a statistically hard p-threshold. This is an understandable situation: the cost of error in these trajectories is high, and the correction itself is simple and accepted quickly. Clopidogrel required replacement primarily in patients with delayed CYP2C19, whereas warfarin benefited from a more cautious starting dose and early INR control.

The statin and beta-blocker trajectories produced a more moderate but quite distinguishable effect. In patients on statins, fewer problematic responses were combined with a higher proportion of achieving the target by week 12. For metoprolol, the benefit was closely related not only to the choice of dose, but also to the rate of titration; here, pharmacogenetics worked as a tool for controlling the rate of treatment, not just the starting dose.

The frequency of the composite endpoint, depending on the presence of a clinically significant profile, is shown in Figure 4.

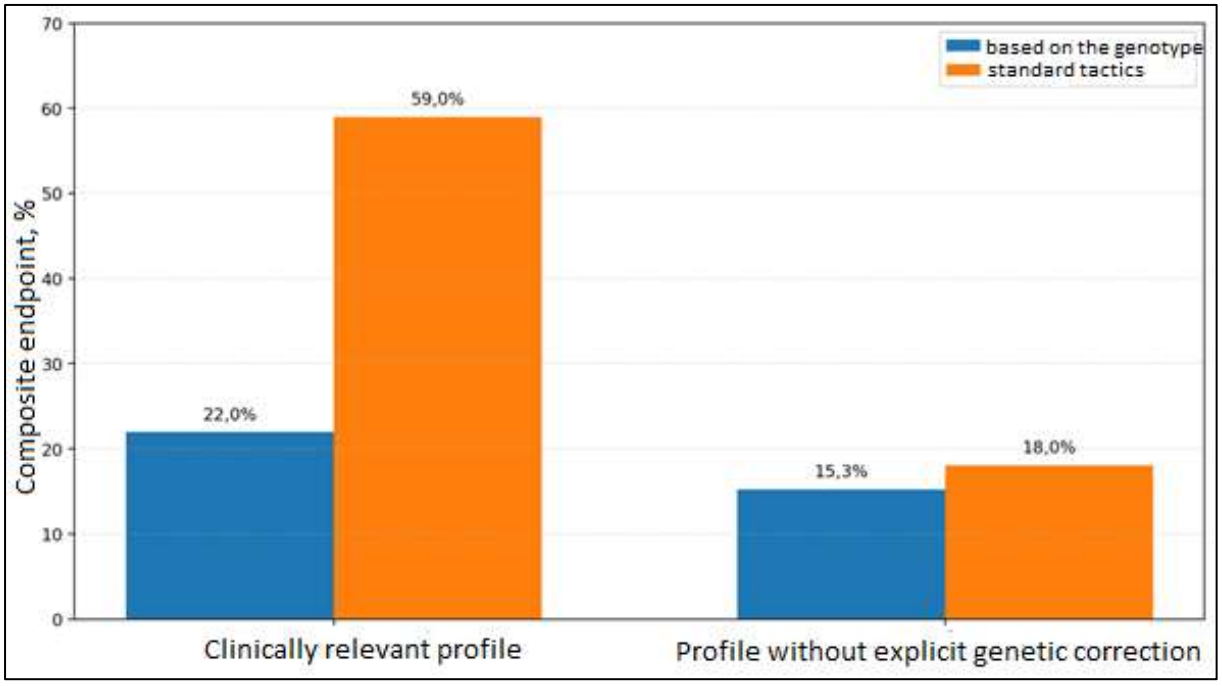

Figure 4 – Frequency of composite endpoint depending on the presence of a clinically significant profile

Among carriers of a clinically significant profile, the incidence of a problematic outcome decreased from 59.0% to 22.0% (p=0.001), whereas in patients without an obvious genetic reason for intervention, the difference between the subgroups was small (p=0.808). This piece of analysis is especially useful for discussing the economic side of the issue: not everyone gets the most out of it, but the part of the flow where the test really changes purpose.

If you look at the question more broadly, launching a panel for the entire drug formulation at once is not always justified. It is much more reasonable to start with routes where the frequency of a clinically significant profile and the cost of error are particularly high: clopidogrel, warfarin, then statins and metoprolol. Such a phased launch reduces the burden on the laboratory and makes the implementation effect more visible to the clinic administration [1].

Below is a scheme that is suitable for a multidisciplinary clinic and can be used for internal regulations.

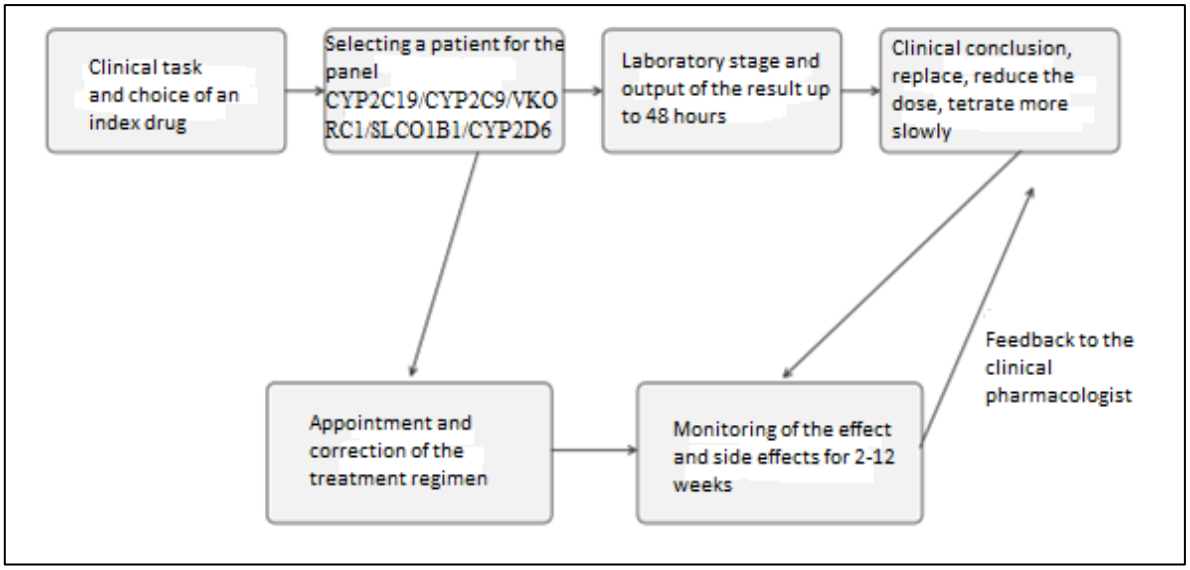

Figure 5 – The route of genotype-based drug administration in a multidisciplinary clinic

The scheme highlights three bottlenecks. The first is the time when the result is given: if the interpretation comes too late, the initial decision has already been made and the inertia of the assignment turns out to be stronger than the genotype. The second is the form of the conclusion. Doctors do not need a list of alleles, but a short clinical formula: replace, reduce the dose, titrate more slowly, leave unchanged. The third is the obligatory feedback loop, when the patient's outcome returns to the clinical pharmacologist and clarifies the local algorithm.

At this stage, pharmacogenetics ceases to be just a laboratory service, it becomes part of the patient's route, almost as routine as INR or lipid profile monitoring. If such a route is not described in advance, testing remains an episode. If it is integrated into the flow, the genotype turns into a working tool for assignment [7].

A narrower starting scenario is also possible, when the panel is not prescribed to everyone, but to patients with polypragmasia, unstable INR, episodes of early drug intolerance, planned clopidogrel administration after surgery, or muscle symptoms on the background of statins. For a regional clinic, this path often turns out to be more realistic than total screening.

CONCLUSION

In the presented study of 200 observations, a clinically significant pharmacogenetic profile was found in 40.0% of patients. This figure alone shows that we are not talking about rare incidents, but about a recurring clinical situation.

The densest genetic signal was obtained in the warfarin route, where the combination of CYP2C9 and VKORC1 particularly often required a revision of the starting dose. For clopidogrel, statins, and metoprolol, the benefits were also noticeable, although the mechanism of intervention varied: the drug changed somewhere, and the titration rate changed somewhere.

The genotype-based tactics were accompanied by a decrease in the composite drug-associated endpoint from 34.0% to 18.0% and an earlier achievement of the clinical goal. The practical effect was already visible in the first weeks of follow-up, and not just by the end of the 12-week period. Among patients with a clinically significant profile, the differences between the strategies were particularly pronounced: 59.0% versus 22.0%. This means that it is not abstract testing per se that gives the greatest benefit, but the exact placement of the test in the group where it really changes its purpose.

To implement pharmacogenetics in a multidisciplinary clinic, a short laboratory cycle, a single clinical conclusion and the participation of a clinical pharmacologist at the interpretation stage are needed. Without such a bundle, even the correct genotype loses a significant part of its usefulness, which is clearly seen by the two unrealized recommendations in the main subgroup.

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