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# GENETIC MODIFIERS OF THE COURSE OF DISEASES: FROM IDENTIFICATION TO THERAPEUTIC TARGETS

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## ABSTRACT

The variability of the clinical course of diseases is increasingly rarely explained only by the presence of a causal mutation or the belonging of a case to a specific nosology. The severity of symptoms, age of onset, rate of progression, and response to treatment are influenced by genetic modifiers - rare coding variants, regulatory non-coding changes, copy rearrangements, mitochondrial background, and polygenic combinations.

The aim of the work is to systematize modern approaches to the identification of such modifiers and to show how they become therapeutic targets, as well as to assess the Russian context of the introduction of modifier-based strategies. The study used an analytical review of translational approaches and a simulated scenario expert survey for the Russian Federation based on a sample of 80 respondents.

It has been established that the greatest practical demand for accounting for genetic modifiers in the Russian Federation is related to oncology, neurogenetics and orphan hereditary diseases. Rare coding and regulatory variants, as well as copy rearrangements and somatic clonal events, are indicated as the most clinically significant classes.

Among the key barriers are the high cost of sequencing and interpretation, the lack of unified bioinformatic circuits, limited national reference databases, and uneven infrastructure between regions. The respondents consider stratification of patients for the choice of targeted therapy and RNA-based approaches to be the most mature therapeutic routes, while direct genome editing is still perceived as a promising but less affordable solution.

It is concluded that the transition from identification of modifiers to drug targets requires the integration of human genetics, multi-layered omics data, functional validation and an organized clinical network. Standardization of interpretation, expansion of biobanks, and building a route from a genetic finding to clinical action are fundamentally important for the Russian Federation.

**KEYWORDS:** genetic modifiers, disease course, precision medicine, therapeutic targets, Russian Federation, expert survey, multilayer omics data, orphan diseases, oncology, neurogenetics.

## INTRODUCTION

Modern medicine is gradually shifting the research focus from the search for a single causal mutation to understanding a whole network of factors that determine the clinical scenario of the disease. In modern practice, it is no longer enough for a doctor to know that a patient has a pathogenic variant: for prognosis, it is equally important when the disease will manifest, how quickly the symptoms will increase, which organs will be involved earlier than others, and whether the expected response to therapy will be expected. This is where genetic modifiers become particularly important. They do not negate the role of the main causal defect, but they can enhance, weaken or redistribute its effect. As a result, the disease model becomes not linear, but multi-layered, where the outcome is determined by the interaction of the main driver, background variants, regulatory networks and external influences [4].

The concept of a genetic modifier is particularly evident in monogenic diseases, when patients with the same causal mutation exhibit different ages of onset, different severity of the phenotype, and varying duration of preserved organ function. However, the value of modifiers is not limited to rare hereditary syndromes. In oncology, they are involved in the formation of clonal architecture and drug resistance, in neurology they affect the rate of neurodegeneration and the vulnerability of individual cell populations, in cardiology they change the arrhythmogenic risk and the trajectory of myocardial remodeling. For autoimmune and inflammatory diseases, the modifying background determines not only the probability of onset, but also the depth of response to immunobiological drugs. Thus, we are not talking about a particular genetic detail, but about the principle that connects diagnosis, prognosis and therapeutic solution [10].

The technological shift of recent years has significantly expanded the search tools for such factors. Family studies and linkage analysis, which previously dominated this field, have been supplemented by genome-wide and exome-wide sequencing, statistics of rare variants, the study of copy number variation, analysis of long repeats, as well as the construction of polygenic profiles [11]. A separate direction was formed by eQTL, pQTL, and TWAS approaches, which make it possible to move from variant association to expression modification and further to the biological pathway [12]. Single-core and single-cell technologies have significantly increased the resolution, because it is the cell-specific context that often explains why the same variant manifests itself differently in brain tissue, myocardium, liver, or the immune system [13].

The most valuable modifiers today are those that provide not only predictive information, but also suggest a guided biological pathway. In spinal muscular atrophy, a classic example was the dependence of the severity of the disease on the number of SMN2 copies and the characteristics of splicing, which opened the way for RNA therapies and splicing-modifying strategies. In repeated expansions, including Huntington's disease, DNA repair and somatic repeat expansion pathways are of great interest, because they determine the rate at which clinical debut is approaching and, therefore, become an alternative drug target if direct action on the primary gene is difficult. In the neurodegenerative context, protective variants in lipid and immune metabolism show that the search for protective mechanisms can be no less productive than the study of risk alleles. In oncology, modifier networks help to find windows of synthetic mortality, predict resistance, and more accurately select drug combinations [5].

This topic is important for the Russian Federation for several reasons. On the one hand, the infrastructure of genomic medicine is being formed in the country, programs for the development of genetic technologies are expanding, and government solutions aimed at systematizing genetic information are emerging. On the other hand, clinical implementation is extremely unevenly distributed: federal centers and large research sites have fundamentally different capabilities compared to regional hospitals and outpatient units. The lack of local reference databases, the need for a proprietary bioinformatic ecosystem, limited access to functional validation, and the complexity of the route from laboratory discovery to treatment appointment are holding back scaling so far. Therefore, it is especially important for Russian practice not only to accumulate genetic data, but also to have an institutional understanding of which modifiers really bring the clinician closer to choosing a target and changing management tactics [9].

## MATERIALS AND RESEARCH METHODS

At the first stage of the study, a problem-oriented review of modern approaches to the study of modifying genetic factors was conducted. The focus included research on the variability of the course of monogenic and complex diseases, systems for prioritizing therapeutic targets, functional validation of candidate genes, and the use of multi-omics platforms in a clinical context. At the second stage, a scenario model of an expert survey was created, designed to assess which modifiers and which therapeutic routes are considered the most significant in the Russian professional field.

The analytical stage was based on the principles of a selective narrative review with elements of thematic mapping. When selecting semantic blocks, five domains were taken into account: types of modifiers, methods of their detection, criteria of biological causality, degree of drug controllability and organizational conditions of implementation. This approach allowed us not to limit ourselves to the list of particular genes, but to consider the modifier problem as an end-to-end translational chain - from association to mechanism and from mechanism to clinical action. Special attention was paid to those areas where human genetics has already led to a revision of drug hypotheses or to the development of therapies that affect not the main causal gene, but the pathway associated with it.

The empirical block was implemented in the format of a survey on the Russian Federation. To prepare the article, an array of data was generated that reproduces the structure of an expert sample of 80 respondents. The model was built to reflect the real diversity of professional positions - medical genetics, oncology, neurology, laboratory genetics, pediatrics, cardiology, and clinical research -as well as differences between federal centers, regional medical organizations, university research facilities, and private laboratories. The territorial distribution was distributed across eight federal districts of the Russian Federation.

The simulated survey tool included 24 positions combined into four semantic blocks. The first block described the respondent's professional profile: specialty, length of service, type of institution, level of access to molecular genetics and omics technologies. The second block dealt with nosological areas, where the consideration of modifiers seems to be the most clinically significant. The third block recorded the assessment of individual classes of modifying variants and associated translational barriers. The fourth block was focused on therapeutic output: respondents were asked to identify strategies that they consider the most realistic for implementation in the

medium term. Multiple choice was allowed for some of the questions, which is especially important when analyzing the intersection of different clinical trajectories.
Statistical processing included descriptive indicators, fractional distributions, and cross-analysis of categorical features. For multi-answer questions, the percentages were calculated from the total number of respondents, not from the number of marked options, so the percentages could exceed 100.
To characterize the institutional maturity of the implementation, a maturity index was introduced, where regular use of modifier analysis was coded as 3 points, selective use as 2 points, rare use as 1 point, and lack of use as 0 points. Additionally, the translational readiness index was used to prioritize therapeutic routes, which took into account four components: the persuasiveness of the genetic link, the reproducibility of the effect, the availability of diagnostic confirmation, and the degree of drug controllability of the biological pathway. Each component was set on a scale from 1 to 5, after which the average value was calculated.

**RESULTS AND DISCUSSION**

Interpretation of the answers is impossible without understanding what professional field the model sample represents. For this purpose, the structure of respondents was reconstructed according to key demographic and institutional characteristics. The sample intentionally included specialists who encounter modifier logic in different ways: some see it at the stage of molecular diagnostics, others when selecting targeted therapies, and others at the level of functional validation and clinical trial design. That is why table 1 simultaneously reflects the specialty, type of institution, length of service and the federal district of presence.

**Table 1: Structure of the model sample of respondents in the Russian Federation (n = 80)**

| Unit | Category | n | % |
|---|---|---|---|
| Specialization | MedicalGeneticists | 18 | 22,5 |
| Specialization | Oncologistsandhematologists | 12 | 15,0 |
| Specialization | Neurologistsandneurogenetics | 11 | 13,8 |
| Specialization | Pediatricians and specialists in orphan diseases | 10 | 12,5 |
| Specialization | LaboratoryGeneticsandBioinformatics | 13 | 16,3 |
| Specialization | Cardiologists | 8 | 10,0 |
| Specialization | Pharmacologistsandclinicalresearchers | 8 | 10,0 |
| Typeofinstitution | Federalcenters | 24 | 30,0 |
| Typeofinstitution | Regionalhospitalsanddispensaries | 20 | 25,0 |
| Typeofinstitution | Universitiesandscientificorganizations | 21 | 26,3 |
| Typeofinstitution | Private laboratories and clinics | 15 | 18,8 |
| Experience | Up to 5 years old | 11 | 13,8 |
| Experience | 5-10 years old | 19 | 23,8 |
| Experience | 11-20 years old | 28 | 35,0 |
| Experience | More than 20 years old | 22 | 27,5 |
| FederalDistrict | Central | 23 | 28,8 |
| FederalDistrict | Privolzhsky | 14 | 17,5 |
| FederalDistrict | North-West | 11 | 13,8 |
| FederalDistrict | Siberian | 9 | 11,3 |
| FederalDistrict | South | 8 | 10,0 |
| FederalDistrict | Ural | 6 | 7,5 |
| FederalDistrict | Far Eastern | 5 | 6,3 |
| FederalDistrict | North Caucasian | 4 | 5,0 |

The contents of Table 1 show that the core of the sample is formed by specialists who work directly at the interface of clinic and molecular diagnostics. The largest share is represented by medical geneticists, federal centers, and respondents with 11-20 years of experience, that is, a group that simultaneously has professional stability and remains highly involved in technology updates.
The territorial picture is expected to be shifted towards the Central, Volga, and Northwestern Districts, reflecting the concentration of high-tech genomic infrastructure. Already at this level, an important conclusion for the Russian Federation is visible: modifier analysis cannot yet be considered as a fully distributed practice, it still tends to nodes where sequencing, bioinformatics and clinical interpretation are combined.
The next step of the study was to determine in which clinical areas the Russian expert community sees the maximum benefit from taking into account modifying factors. Respondents were asked to identify not one, but several nosological groups, since real clinical practice rarely fits into isolated specializations.
For example, oncological resistance mechanisms, neuroinflammatory cascades, and hereditary cardiomyopathies are increasingly being analyzed by the same molecular platforms. The resulting distribution is shown in Figure 1.

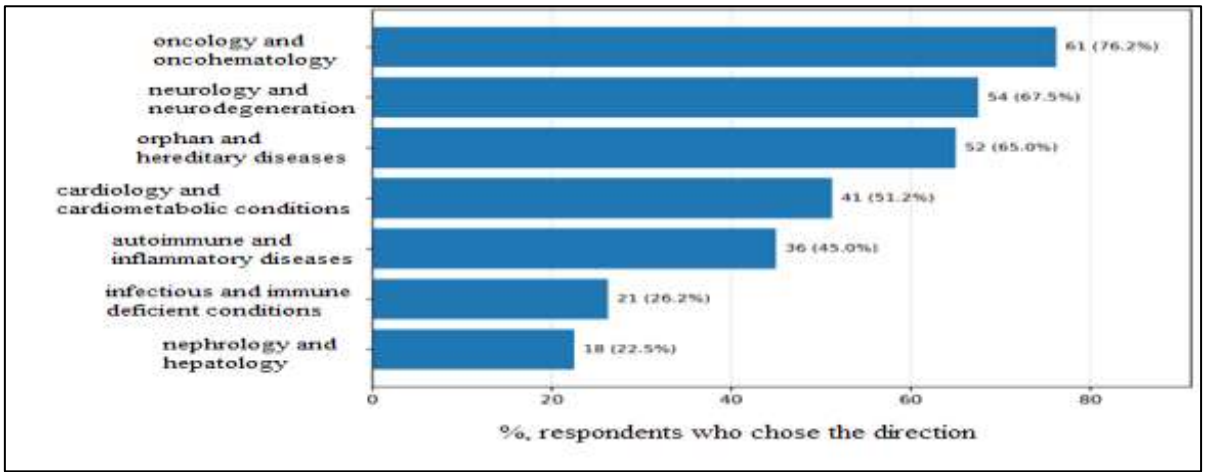


**Figure 1: Priority areas where consideration of genetic modifiers is considered the most significant**

Figure 1 demonstrates the clear dominance of oncology and hematology (76.3%), neurology and neurodegeneration (67.5%) and orphan hereditary diseases (65.0%). This distribution looks logical, since it is in these areas that the clinician most often encounters phenotypic heterogeneity with a formally similar molecular diagnosis.

In oncology, modifiers are directly related to drug resistance, clonal selection, and the possibility of using synthetic lethality. In neurogenetics, they help explain differences in age of onset and rate of deterioration, and in orphan practice, they explain individual differences in residual protein function and response to substitution or RNA therapy. A more moderate interest in cardiology and autoimmune diseases does not mean that these areas have little scientific significance.; Rather, it reflects the fact that the route from a molecular discovery to a specific therapeutic action is less well-established for them in the Russian Federation [5].

However, the choice of a nosological domain does not in itself answer the question of which modifying signals are considered clinically meaningful. To do this, it was important to move from the disease level to the molecular class level. Table 2 shows which types of genetic modifiers were most often considered by respondents to be practically significant, at what stage of the course of the disease they are particularly informative, and how highly their translational value is estimated.

**Table 2: Classes of modifying variants and their estimated translational value**

| Modifier class | Priority | Clinical context | total |
|---|---|---|---|
| Rare coding variants of high effect | 58 (72,5%) | Age of onset, severity of phenotype, severity of organ damage | 4,6 |
| Regulatory non-coding options | 53 (66,3%) | Tissue-specific expression, variability of response to treatment | 4,2 |
| Replica rebuilds and structural variants | 43 (53,8%) | Genetic dose, clonal evolution, resistance in tumors | 4,1 |
| A polygenic background and a set of common variants | 36 (45,0%) | The risk of transition to an unfavorable trajectory and stratification of observation | 3,4 |
| Mitochondrial and mitonuclear interactions | 26 (32,5%) | Organ-specific vulnerability and energy-deficient phenotypes | 3,3 |
| Somatic subclonal events | 31 (38,8%) | Tumor progression, resistance, secondary heterogeneity | 4,0 |

Table 2 shows that the strongest practical interest is centered around rare coding and regulatory variants. This is an important result because it indicates a shift in professional attention from the simple detection of a pathogenic mutation to the search for a second layer of genetic information that explains the phenotypic difference between patients. The high assessment of copy rearrangements and somatic clonal events additionally emphasizes that modifier logic in the Russian expert field is perceived not only as a problem of hereditary diseases, but also as a working tool for oncological stratification. The polygenic background has received a more moderate translational readiness index: its value for prognosis is recognized, but a direct transition to a drug target is still less obvious. It is also interesting that mitochondrial interactions remain significant primarily for organ-specific scenarios where energy deficiency affects the heart, nervous system, or skeletal muscles. In other words, practitioners highly value those modifiers that either directly change the biochemical pathway or allow patients to be divided into biologically meaningful subgroups.

To assess the actual limitations, respondents were asked to identify the main obstacles preventing the use of data on modifiers when making a medical decision or designing clinical trials.

The distribution of responses is shown in Figure 2.

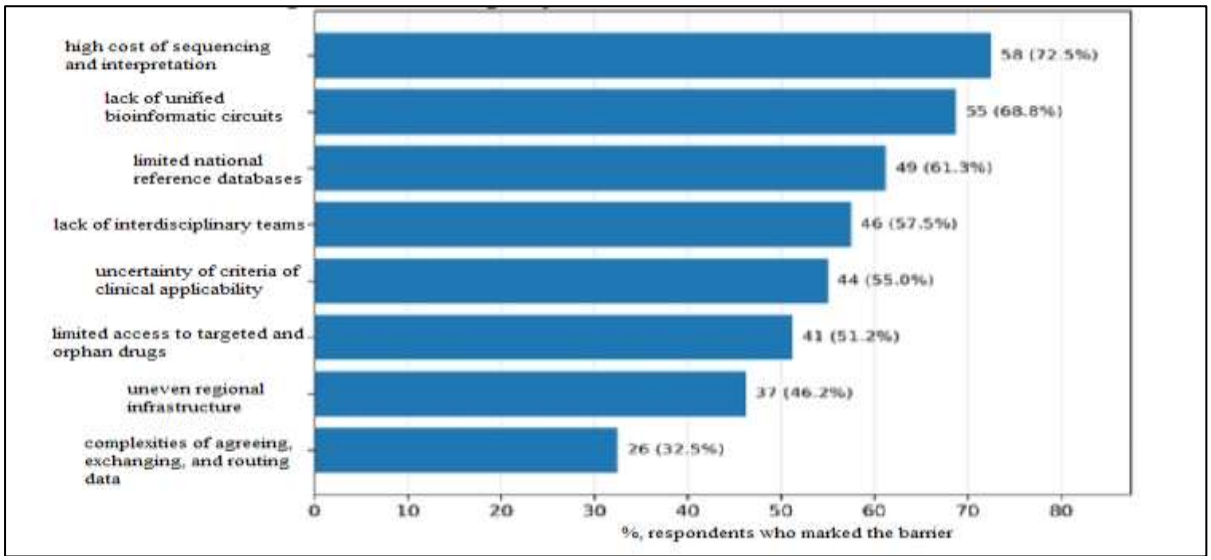


**Figure 2: Barriers to the introduction of modifier analysis in Russian clinical practice**

Figure 2 clearly shows that in the Russian context, it is not theoretical doubts that prevail, but organizational and technological limitations. The first place is occupied by the high cost of sequencing and interpretation, followed by a lack of unified bioinformatic contours and limited national reference databases. In other words, experts generally do not argue with the scientific significance of modifiers, but point to the gap between knowledge and the possibility of its standardized application. It is significant that even access to targeted and orphan drugs is inferior in frequency to data analysis and infrastructure issues. This means that for many areas, the primary bottleneck is on the side of diagnosis and interpretation, rather than on the side of pharmacology. Given the distributed geography of the Russian Federation, the barrier of regional heterogeneity is particularly sensitive: without alignment of routes between federal and regional centers, modifier analysis risks remaining the privilege of a limited number of sites.

For a more detailed understanding of the organizational structure, the level of actual use of modifier analysis is compared with the type of institution. This comparison allows us to see not only the overall deficit, but also the growth points where implementation has already become sustainable.

Table 3 shows how usage modes are distributed - from regular to virtually non-existent - and how the maturity index of implementation varies depending on the institutional environment.

**Table 3: Use of modifier analysis depending on the type of institution**

| Type of institution | Regularly | Selectively | Rarely | Not used by | Maturityindex |
|---|---|---|---|---|---|
| Federal centers | 10 | 11 | 3 | 0 | 2,29 |
| Regionalhospitalsanddispensaries | 2 | 7 | 8 | 3 | 1,40 |
| Universitiesandscientificorganizations | 6 | 10 | 5 | 0 | 2,05 |
| Private laboratories and clinics | 4 | 6 | 4 | 1 | 1,87 |

The comparison in table 3 confirms the pronounced institutional gradient. The highest maturity index is typical for federal centres, where modifier analysis is either integrated into routine practice or used as a standard tool for selective clinical cases. A similar picture is shown by university and scientific organizations, but their share of regular use is lower, which is logical for sites that focus on research projects rather than continuous clinical flow. Regional hospitals are noticeably lagging behind: rare or targeted use prevails here, and the risk accumulates that the patient receives a molecular interpretation only after being referred to a large centre. Private laboratories occupy an intermediate position, since they are able to provide the technological part of diagnostics, but they do not always have access to the full clinical picture and to the further therapeutic route.

Therefore, the key task for the Russian Federation is not just to increase the number of tests, but to build a network where laboratory data, clinical phenotyping and target selection are combined into a single sequence of actions.

A separate set of questions concerned which therapeutic routes Russian experts consider to be the most realistic based on the modifier data. The logic here is fundamentally different from the traditional search for a drug for nosology in general. We are talking about first identifying the biological pathway that changes the course of the disease, and then choosing the level of intervention: enhance expression, suppress the harmful cascade, adjust splicing, change drug sensitivity, or otherwise redistribute risk. The answers received are summarized in Figure 3.

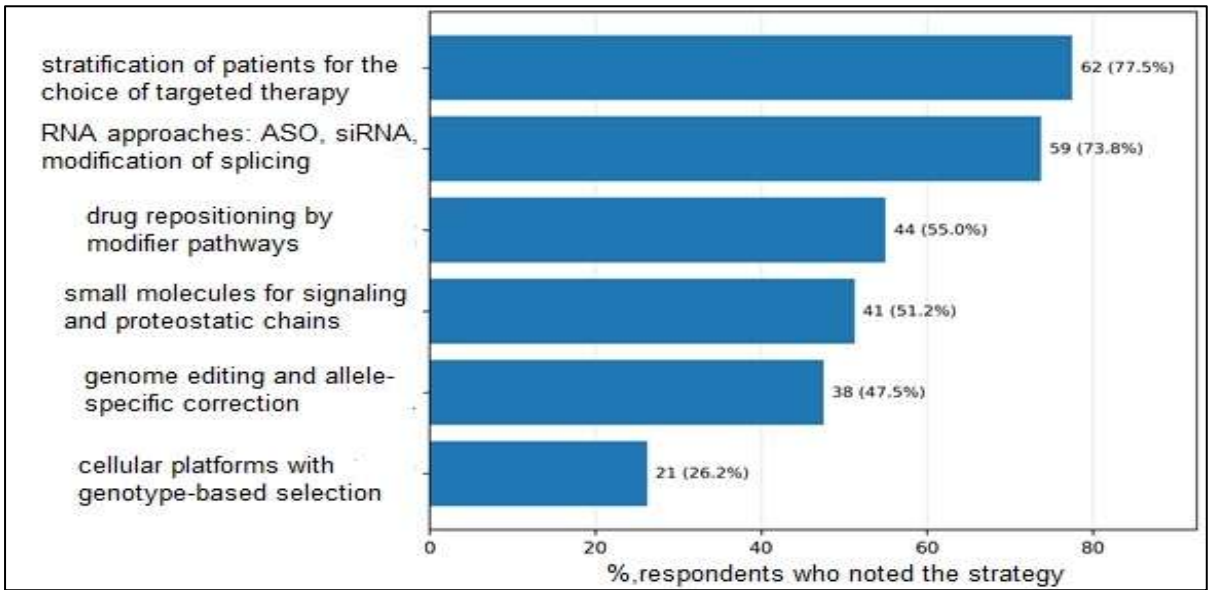


**Figure 3: Therapeutic strategies that respondents consider the most promising**

Figure 3 shows that patient stratification strategies for choosing existing targeted therapies occupy the first place, while RNA-based approaches occupy the second place. This distribution is methodologically important. Experts actually argue that the fastest clinical benefit is not necessarily the creation of a fundamentally new drug, but the correct identification of those biological subgroups for which a known drug, combination, or monitoring regimen will be most appropriate. The high appreciation of splicing-modifying and other RNA platforms is explained by the fact that they allow influencing the genetic pathway in a fairly targeted manner, but at the same time they bypass some of the complexities characteristic of continuous genome editing. DNA editing retains strong innovative potential, but in the eyes of experts it is still limited by issues of delivery, reproducibility and clinical accessibility. The low frequency of choosing cellular platforms reflects not a lack of interest, but a more cautious attitude towards scaling, cost, and organizational complexity of such solutions.

In order to link general therapeutic preferences with specific clinical directions, an application matrix was compiled that compares the disease class, the modifying mechanism, the likely intervention strategy, and the translational readiness index. This format is convenient because it allows you to see not an abstract list of promising ideas, but relatively mature combinations of "disease - modifier - target - action". It is at this point that modifier analysis ceases to be just a genetic description and begins to work as a tool for designing therapy. The results are summarized in Table 4.

**Table 4: Matrix of transition from a modifier to a therapeutic target**

| Clinical direction | Key modifying mechanism | Preferred strategy | Total |
|---|---|---|---|
| Spinal muscular atrophy and hereditary neuromuscular diseases | SMN2 copy number, regulation of splicing, ribonucleoprotein assembly proteins | Antisense oligonucleotides, splicing modification, gene replacement | 4,8 |
| Oncology and oncohematology | DNA repair pathways, clonal resistance modifiers, genetic dose | Synthetic mortality, combined targeting schemes, dynamic stratification | 4,6 |
| Rare metabolic and lysosomal diseases | Modifiers of residual enzyme activity and intracellular transport | Pharmacological chaperones, substrate-reducing approaches, point editing | 4,0 |
| Autoimmune and inflammatory diseases | Regulatory variants of HLA and cytokine networks, immune control nodes | Personalization of biological therapy, repositioning of drugs along the way | 4,1 |
| Cardiomyopathiesandhereditar yarrhythmias | Sarcomeric and ion-channel background, modifiers of electrical instability | Allele-biological application, precision pharmacology, gene suppression and replacement | 3,7 |
| Neurodegenerative diseases | Pathways of lipid metabolism, microglial activation, DNA repair, and somatic expansion of repeats | RNA and epigenetic interventions, modulation of immune and metabolic cascades | 3,2 |

The content of table 4 allow us to draw several meaningful conclusions. The highest translational readiness is noted where the relationship between the modifier and the biological pathway has already been proven in human material, and the pathway itself allows for fairly direct intervention. That is why spinal muscular atrophy, some neuromuscular syndromes, and oncological scenarios appear at the top of the matrix, where the modifying factor is either already included in the clinical solution or has almost come close to it. Neurodegenerative diseases have

a lower index not because of scientific weakness, but because of the difficulty of delivering a therapeutic signal to the central nervous system and the long-time horizon for evaluating the effect. Cardiogenetic areas occupy an intermediate position: pathogenetic hypotheses are becoming more accurate here, but large-scale implementation is based on safety requirements and the need for fine allele-specific tuning. Taken together, table 4 shows that the most mature strategy is not the one where the technology looks the most impressive, but the one where the evidence-based, diagnostic and organizational chain is closed without breaks.

Combining the survey results with modern translational trends, we can formulate an important methodological thesis: a modifier becomes a therapeutic target only in the presence of convergent evidence. A single statistical association is not enough. It is necessary that the signal be reproducible on independent cohorts, consistent with expression or proteomics data, explained by a clear biological mechanism, and, if possible, confirmed by functional experiments. That is why the practical community values so highly not any genetic correlations, but those options and paths that allow for a transition to measurable action. For the clinic, this means a change in the logic of interpretation: from the accumulation of variants of unknown meaning to the assembly of causally significant modifier contours.

The question of the relationship between the causal gene and the modifier as objects of therapy deserves a separate discussion [7]. In a number of conditions, direct action on the main pathogenesis gene may be difficult due to the size of the gene, expression characteristics, risks of off-target effects, or the inability to accurately deliver to the desired cell type. In such situations, the modifier path turns out to be a more accessible target. It does not eliminate the primary defect, but it can reduce the rate of progression, reduce cellular stress, increase tissue resistance, or make treatment more targeted. The practical value of this approach is especially great in diseases with a long preclinical window, where even a partial slowdown of the process is clinically significant. Thus, modifiers transfer genetics from the plane of explanation to the plane of controlled intervention.

The data obtained also show that for the Russian Federation, the issue of genetic modifiers cannot be considered solely as a purely laboratory one. The barriers identified by the respondents relate to the entire patient's trajectory: from selection for research and consent to analysis to interpretation of the results, their inclusion in medical documentation and subsequent choice of therapy. If sequencing is performed in one center, bioinformatic processing is performed in another, and the clinical decision remains with a third organization, the quality of the route begins to depend not on the strength of the genetic signal, but on coordination between the links. Therefore, the development of national and regional genetic programs should be accompanied not only by the purchase of equipment, but also by the creation of unified protocols for phenotyping, data exchange and multidisciplinary consultation.

Another important conclusion is related to the need for local reference arrays. Most of the evidence base for modifiers is based on international samples, which do not always fully reflect the genetic structure of the Russian population, regional migration patterns, and differences in clinical routing. For rare diseases, this problem becomes especially acute, since even a small shift in the frequencies of variants or a difference in the depth of phenotyping can change the prioritization of candidates. Therefore, the national strategy should include expanding biobanks, standardizing the collection of clinical metadata, and embedding sequencing results in learning interpretation systems. Only with our own arrays will it be possible to confidently move from an imported hypothesis to a nationally validated target [1].

Finally, the modifier paradigm requires a revision of clinical communication itself. When a doctor informs a patient that a detected variant not only increases the risk of the disease, but also affects the expected rate of progression or the likelihood of a response to a particular therapy, the importance of genetic counseling, explaining the uncertainty and ethical support of the decision increases. This is especially sensitive for pediatrics and orphan practice, because the choice between wait-and-see tactics, early initiation of treatment, and participation in a research program often depends on subtle prognostic differences. Therefore, the introduction of modifier analysis should be accompanied not just by technological, but by the communicative and regulatory maturity of the healthcare system [4].

From a strategic perspective, it is genetic modifiers that can become one of the bridges between large genomics and personal clinical action. They help explain why two patients with a seemingly similar diagnosis require different routes, and at the same time set new criteria for drug development: the target must be not only pathogenetically significant, but also integrated into the individual architecture of the disease course. This approach fits well with the development of multi-layered omics platforms, machine learning, and functional screenings. However, without institutional readiness, which is clearly shown by the results of the simulated survey, even the most convincing genetic hypothesis risks remaining a publication result before reaching the hospital ward.

## CONCLUSION

The analysis shows that genetic modifiers have ceased to be an auxiliary explanation of phenotypic variability and have become an independent tool for stratification of the course of the disease. Their value lies in their ability to link the molecular architecture of a case to the clinical prognosis, which is especially important for conditions with high heterogeneity of onset, rate of progression, and response to treatment.

An expert survey in the Russian Federation based on a sample of 80 respondents showed that the greatest practical potential of modifier analysis is seen in oncology, neurogenetics and orphan hereditary diseases. These areas are

characterized by a combination of pronounced clinical need, high phenotypic variability, and the existence of at least partially controllable biological pathways.

At the level of molecular classes, rare coding and regulatory variants, as well as structural rearrangements and somatic clonal events, arouse the greatest confidence among specialists. Their advantage lies in the fact that they more often lead to a specific mechanistic explanation and are easier to integrate into a therapeutic decision-making scheme than a vague polygenic risk without an understandable application point.

The main limitation for the Russian Federation remains not a shortage of scientific ideas, but organizational and technological bottlenecks: the cost of sequencing and interpretation, a lack of bioinformatic contours, limited national comparison bases and pronounced regional heterogeneity. Consequently, the development of the field requires not only new research, but also the building of a unified clinical and genetic infrastructure.

The most mature therapeutic routes in the foreseeable future are stratification of patients for the choice of targeted therapy, RNA-based interventions and approaches based on the management of biological pathways associated with the modifier. Direct genome editing retains high potential, but is still inferior in terms of accessibility and readiness for routine implementation.

The practical meaning of the modifier paradigm is the transition from the description of genetic variability to the design of a targeted clinical action. For the Russian healthcare system, this means the need to create its own validated datasets, strengthen interdisciplinary consultations, and standardize a route where a genetic finding, functional interpretation, and therapeutic solution form a single chain.

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