Оригинальное исследование | Original study article
DOI: https://doi.org/10.35693/SIM646475

Predictors of successful molecularly targeted therapy based on comprehensive genomic profiling data

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Abstract

Aim – to study predictors of successful performance of comprehensive genomic profiling and prescription of molecular targeted therapy for patients with advanced solid tumors.

Material and methods. We performed a retrospective single-center study of data of 104 patients who underwent comprehensive genomic profiling by targeted sequencing in the period of 2019 to 2023. The assessment of clinical significance of the identified genome alterations was performed using the scale for clinical actionability of molecular targets of the European Society for Medical Oncology (ESCAT). Analysis were performed of the mutation spectrum, efficiency of molecular targeted therapy, and its effect on survivability. Methods of logistical regression were used for the statistical analysis.

Results. Comprehensive genomic profiling was successfully performed in 87 patients (83.7%). Potentially targeted alterations were found in 44.8% patients, of which 11 persons received molecular targeted therapy. The main predictors of successful performance of comprehensive genomic profiling were the sufficient volume of tumors and lower number of revisions of biological material. Among the patients who received molecular targeted therapy, the overall median survival in the groups was 58 weeks as compared to the 35 weeks in the group of patients without molecular targeted therapy (p=0.097). In three patients, extraordinary response was noted.

Conclusion. The findings show clinical relevance of comprehensive genomic profiling in personalized treatment of solid tumors. The obtained data emphasize the need for careful selection of patients for comprehensive genomic profiling to improve its efficiency and availability.

Keywords: predictors, comprehensive genomic profiling, solid tumors, next generation sequencing, molecularly targeted therapy.

Conflict of interest: nothing to disclose.

Citation
Shilo PS, Makarkina ML, Zakharenko AA. **Predictors of successful molecularly targeted therapy based on comprehensive genomic profiling data.** *Science and Innovations in Medicine*. 2025;10(1):63-68.
DOI: https://doi.org/10.35693/SIM646475

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Received: 03.01.2025
Accepted: 06.02.2025
Published: 12.02.2025

Предикторы успешной молекулярно-направленной терапии на основании данных комплексного геномного профилирования

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Аннотация

Цель – изучить предикторы успешного выполнения комплексного геномного профилирования и назначения молекулярно-направленной терапии у пациентов с распространенными солидными опухолями.

Материалы и методы. Проведено ретроспективное одноцентровое исследование данных 104 пациентов, которым с 2019 по 2023 годы выполнено комплексное геномное профилирование методом таргетного секвенирования. Для оценки клинической значимости выявленных геномных альтераций использована классификация ESCAT. Проведен анализ спектра мутаций, эффективности молекулярно-направленной терапии и ее влияния на выживаемость. Для статистического анализа применялись методы логистической регрессии.

Результаты. Комплексное геномное профилирование было успешно выполнено у 87 пациентов (83,7%). Потенциально таргетируемые альтерации выявлены у 44,8% пациентов, из которых 11 человек полу-

чили молекулярно-направленную терапию. Основными предикторами успешного выполнения комплексного геномного профилирования стали достаточный объем опухолевой ткани и меньшее количество пересмотров биоматериала. У пациентов, получивших молекулярно-направленную терапию, медиана общей выживаемости в группах составила 58 недель в сравнении с 35 неделями в группе пациентов без молекулярно-направленной терапии (p=0,097). Экстраординарный ответ наблюдался у 3 пациентов.

Заключение. Результаты исследования демонстрируют клиническую значимость комплексного геномного профилирования в персонализированном лечении солидных опухолей. Полученные данные подчеркивают необходимость тщательного отбора пациентов для комплексного геномного профилирования, что позволит повысить его эффективность и доступность.

Ключевые слова: предикторы, комплексное геномное профилирование, солидные опухоли, секвенирование нового поколения, молекулярно-направленная терапия.

Конфликт интересов: не заявлен.

Для цитирования:
Шило П.С., Макаркина М.Л., Захаренко А.А. **Предикторы успешной молекулярно-направленной терапии на основании данных комплексного геномного профилирования.** *Наука и инновации в медицине.* 2025;10(1):63-68.
DOI: https://doi.org/10.35693/SIM646475

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КПГ – комплексное геномное профилирование;
МНТ – молекулярно-направленная терапия.

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Получено: 03.01.2025
Одобрено: 06.02.2025
Опубликовано: 12.02.2025

INTRODUCTION

Despite today's achievements in the sphere of oncology, the prognosis of patients with advanced forms of malignant tumors remains negative. Five-year survival in pancreatic cancer with remote metastases is approx. 3%, for patients with colonic carcinoma it is 13%, and for female patients with breast cancer, approx. 30% [1, 2].

The high incidence rate of solid tumors identified in the locally disseminated and metastatic stages, and poor outcomes of treatment account for the necessity of search for additional therapeutic options for this category of patients.

One of prospective approaches is the comprehensive genomic profiling (CGP) and prescription of molecular targeted therapy (MTT) based on the results of this diagnostic test. CGP allows to increase the number of potentially targeted alterations, i.e. biological events that may be the targets of the respective targeted therapy. In 51.7-99% of patients with disseminated forms of tumors who undergo such profiling, changes are identified that may be aligned with a registered targeted therapy or a clinical trial focusing on MTT [3-7].

The advent of such technologies makes oncologists face numerous new diagnostic and clinical tasks: high cost of diagnostics, difficulty of interpretation of results account for the necessity of finding a group of patients who would receive the maximum benefit from profiling.

AIM

To find predictors of targeted alterations by using comprehensive genomic profiling and predictors of successful molecular targeted therapy.

MATERIAL AND METHODS

In the single-center retrospective study, data were analyzed from 104 patients who underwent tumor tissue CGP using technologies of tumor genome sequencing. The patients were under observation in the oncology department of the "Lakhta" (formerly "Luch") clinic from 2019 to 2023. The decision of performing the new generation sequencing (NGS) and prescription of MTT was made jointly within the framework of oncology consultations. CGP was performed my method of targeted sequencing using large size (>300 genes) commercially available panels (OncoAtlas, FoundationOne). The identified genome alterations were classified using the ESCAT criteria to assess the level of their clinical significance [8].

The study included the analysis of the range of mutations, prescription of targeted therapy based on molecular data, evaluation of the clinical response of the tumor, and study of patient survival rates on the background of treatment. To identify predictors of successfully performed CGP, as well as predictors of successful MTT, statistical analysis was performed with multivariate logistic regression.

RESULTS

General characteristics of the cohort

CGP was performed for 104 patients, and successful results were obtained for 87 people (83.7%). The baseline parameters of this cohort of patients are shown in **Table 1**.

The following are identified as the prevalent oncological diseases: breast cancer (n=20, 23%), colorectal cancer (n=19, 21.8%) and pancreatic cancer (n=7, 8%). The average age of patients at the moment of profiling was 57 years. All patients included in the study had either the primary diagnosed metastatic stage of the disease, or the progression of the earlier localized process.

The data on the number of lines of previous therapy were available for 79 patients. 33 patients (41.8%) had received three and more lines of therapy. Atlas Solo (n=43, 49.4%) and FoundationOne (n=39, 44.8%) were the most frequently used diagnostic panels.

Characteristics of identified alterations

The CGP method revealed alterations in 74/87 patients (85.1%). These alterations were potentially targetable in

		Number	%
Diagnosis	Pulmonary adenocarcinoma	5	5.7%
	Colorectal cancer	19	21.8%
	Melanoma	3	3.4%
	Tumor metastasis from unknown primary site	1	1.1%
	Bile duct tumor	3	3.4%
	Tumor of the central nervous system	2	2.3%
	Head and neck cancer	1	1.1%
	Gastric cancer	6	6.9%
	Breast cancer	20	23.0%
	Pancreatic cancer	7	8.0%
	Salivary gland cancer	1	1.1%
	Cervical cancer	1	1.1%
	Ovarian cancer	4	4.6%
	Rare subtypes of cancer	8	9.2%
	Soft tissue sarcoma	5	5.7%
	Squamous cell lung cancer	1	1.1%
Number of lines of therapy prior to comprehensive genomic profiling	0-2 lines of therapy	46	58.2%
	3 and more lines of therapy	33	41.8%
ECOG status	0-1	29	44.6%
	2-3	36	55.4%
Name of diagnostic test	Atlas Solo	43	49.4%
	FoundationOne	39	44.8%
	Other	5	5.7%
Year of performance of diagnostic test	2020	26	29.9%
	2021	20	23.0%
	2022	19	21.8%
	2023	22	25.3%

Table 1. *Baseline characteristics of patients included in the study*
Таблица 1. *Базовые характеристики пациентов, включенных в исследование*

39 patients (44.8%). In 25 (29.1%) patients, one targeted alteration was found, in 9 (10.5%) patients, two, in 4 (4.7%) patients, three targeted alterations. A detailed distribution of alterations is shown in **Table 2**. In 39/87 (46.4%) cases the targeted alterations detected by CGP could not be detected with conventional diagnostic methods.

Analysis of predictors of unsatisfactory results of comprehensive genomic profiling

CGP was unsatisfactory for 17 patients (16.3% cases). The main reasons for unsatisfactory testing were the insufficient amount of tumor in the block for the analysis and lack of intact DNA for analysis. Among patients with unsatisfactory results, the majority were patients with lung tumors (n=6, 35.3%) and pancreatic tumors (n=5, 29.4%).

Univariate and multivariate logistic regressions were performed to analyze predictors of unsatisfactory results of the testing. The following parameters were assessed: localization of primary tumor, diagnostic panel, number of reviews of biomaterial, availability of only the biopsy material for analysis.

The following were predictors of unsatisfactory results of testing as identified by univariate logistic regression: number of preceding lines of therapy (OR = 2.01, 95% CI [1.10-3.04], p=0.041), number of performed revisions of biomaterial (OR = 3.96, 95% CI [2.42-5.59], p=0.003) and availability of only the biopsy material for analysis (OR=4.31, 95% CI [2.09-6.38], p<0.001). The multivariate analysis showed that the number of preceding lines of therapy was mutually correlated with the number of material revisions. The number of biomaterial revisions

		Number	% for sub-table
Distribution of alterations and medications according to ESCAT	1	38	22.4%
	2	7	4.1%
	3	58	34.1%
	4	67	39.4%

Table 2. *Distribution of detected alterations according to ESCAT*
Таблица 2. *Распределение обнаруженных альтераций по шкале ESCAT*

(OR=3.71, 95% CI [2.19-5.47], p=0.002) and availability of only the biopsy material for analysis (OR=5.32, 95% CI [3.01-7.45], p<0.001) were independent predictors. No statistically significant results in the number of unsatisfactory results depending on the diagnostic panel and diagnosis were found. Detailed information on predictors of unsatisfactory results of CGP are shown in **Table 3**.

Predictors for the prescription of molecularly targeted therapy

Univariate analysis of potential predictors for the prescription of MTT following the results of CGP was performed. It analyzed such parameters as reference to various groups of biomarkers as per ESCAT classification, sex and age of patients, number of preceding lines of therapy and ECOG status at the moment of CGP, and the diagnosis.

The predictors for the prescription of MTT were as follows: biomarker of ESCAT Tier I and II, female sex, age below 40 years (**Table 4**).

It is to be noted that this type of analysis may include more unaccounted factors, e.g., patient's financial and

Parameter		Univariate logistic regression, OR [95% CI]	p-value	Multivariate logistic regression, OR [95% CI]	p-value
Number of preceding lines of therapy	0-2	1 (reference)	0.041	1 (reference)	0.14
	>2	2.01 [1.10-3.04]		1.81 [0.83-2.99]	
Number of performed revisions of biomaterial	1	1 (reference)	0.003	1 (reference)	0.002
	>1	3.96 [2.42-5.59]		3.71 [2.19-5.47]	
Availability of only the biopsy material for analysis	Да	1 (reference)	<0.001	1 (reference)	<0.001
		4.31 [2.09-6.38]			

Table 3. *Predictors of unsatisfactory results in comprehensive genomic profiling*
Таблица 3. *Предикторы неудовлетворительных результатов комплексного геномного профилирования*

Parameter		Univariate logistic regression, OR [95% CI]	p-value
ESCAT scale biomarker reference	III, IV	1 (reference)	0.044
	I, II	1.92 [1.03-3.12]	
Sex	Male	1 (reference)	0.002
	Female	4.08 [2.11-6.39]	
Age	Above 40 years	1 (reference)	0.023
	Below 40 years	3.24 [1.87-5.02]	

Table 4. *Analysis of predictors for the prescription of molecularly targeted therapy*
Таблица 4. *Анализ предикторов назначения молекулярно-направленной терапии*

social status. The multivariate analysis was not possible due to mosaic omission of data and small size of sampling.

Analysis of survival in the mixed cohort of patients

The median overall survival in the mixed cohort of patients after CGP was 42 weeks (95% CI [28.6-55.4]). The medians of overall survival in the groups with and without MTT were 58 weeks and 35 weeks, respectively (**Fig. 1**). At the same time, no statistically significant differences were found, likely due to low number of participants in groups (p=0.097).

It is to be noted that the observed difference of absolute values in the survival between the groups is likely accounted for by single cases of extraordinary response in the group of patients who received MTT.

Cohort of patients receiving MTT

Among the 87 patients, for which the CGP was performed successfully, MTT was prescribed in 11 cases. Detailed clinical characteristics of patients follow in **Table 5**. Based on the results of genomic profiling, molecularly targeted therapy was prescribed to two female patients with breast cancer, two female patients with serous highly differentiated ovarian carcinoma, two male patients with lung adenocarcinoma, one male patient with colorectal cancer, one female patient with ovarian granulosa cell tumor, one female patient with glioblastoma, one female patient with soft tissue sarcoma, and one female patient with gall bladder cancer.

Most frequently, Alpelisib (n=3), Pembrolizumab (n=3) and Olaparib (n=3) were prescribed as medications. In singular cases, Erlotinib (n=1) and Sunitinib (n=1) were prescribed.

In two cases, the full clinical response was achieved: the patient with lung adenocarcinoma and high mutational burden after treatment with pembrolizumab, and the patient with POLE mutation and high mutational burden after a preceding course of treatment. In one case, the patient with colorectal cancer, long-term remission was achieved for over two years, with no signs of disease progression. This case was considered one of extraordinary response to MTT.

DISCUSSION

There are numerous publications assessing the efficiency of CGP. Many non-randomized trials demonstrate better outcomes in patients with disseminated forms of solid tumors with implementation of approaches based on molecular profiling [9-13].

The results of prospective trials are contradictive. For example, in the MOSCATO 01 study, out of 1035 adult patients planned for NGS, only 199 (19%) tested patients received genomic targeted therapy. This percentage is comparable with the highest evaluations obtained in

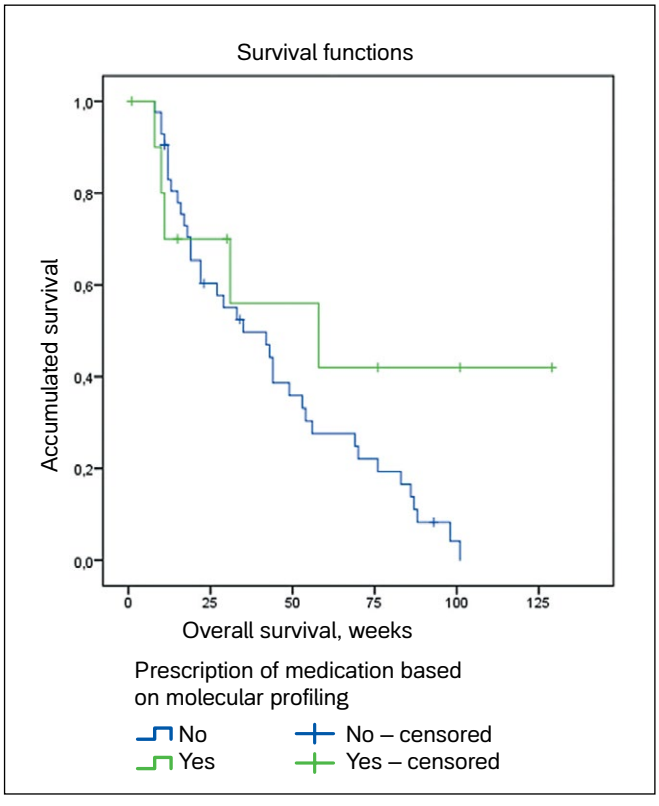

Рисунок 1. *Общая выживаемость в зависимости от факта назначения молекулярно-направленной терапии.*
Figure 1. *Overall survival depending on the administration of molecularly targeted therapy.*

Diagnosis, group	Brief clinical characteristics	Identified alteration	Medication prescribed	Maximum effect of therapy
Breast cancer	39 year old female patient. Triple negative breast cancer (metaplastic carcinoma), after 8 lines of drug therapy	PIK3CA	Alpelisib	Stabilization
Breast cancer	27 year old female patient. Triple negative breast cancer, after 4 lines of drug therapy	High mutational burden (12 mut/Mb)	Pembrolizumab	Progression
Ovarian cancer	42 year old female patient. Serous high-grade ovarian carcinoma.	ATM	Olaparib	Stabilization
Ovarian cancer	38 year old female patient. Serous high-grade ovarian carcinoma.	BRCA2	Olaparib	Partial regression
Lung adenocarcinoma	82 year old female patient. Adenocarcinoma of the upper lobe of the right lung	EGFR	Erlotinib	Partial regression
Lung adenocarcinoma	56 year old male patient. Adenocarcinoma of the upper lobe of the left lung	High mutational burden (12 mut/Mb)	Pembrolizumab	Full clinical response
Colorectal cancer	34 year old male patient. Adenocarcinoma	POLE, TMB	Pembrolizumab	Full clinical response
Ovarian granulosa cell cancer	29 year old female patient. Ovarian granulosa cell tumor, progression against background of 3 lines of drug therapy	CGHCH	Sunitinib	Progression
CNS tumor	55 year old female patient. Glioblastoma of the left parietal lobe, Grade IV, progression against background of 3 lines of drug therapy	PIK3CA	Alpelisib	Progression
Soft tissue sarcoma	28 year old female patient. Leiomyosarcoma of the soft tissue of the face, after 4 lines of drug therapy	BRCA1	Olaparib	Progression
Gall bladder cancer	59 year old female patient. Gall bladder cancer, after 3 lines of drug therapy	PIK3CA	Alpelisib	Stabilization

Table 5. *Clinical characteristics of patients receiving the drug based on molecular profiling data*
Таблица 5. *Клиническая характеристика пациентов, получивших молекулярно-направленную терапию*

specific centers [13]. However, only 22 patients (2.1 %) from the original cohort were able to receive an objective response [14]. Their mOS was 11.9 months. This study also evaluated the PFS2:PFS1 ratio; it was found that this correlation is over 1.3 in 33% of patients. The PFS2:PFS1 ratio >1.3 indicates the advantages of treatment based on CGP, considering that the progression-free time decreases with each line of therapy in the natural progress of the disease.

Another large-scale prospective study (ProfiLER) showed that based on the results of CGP, molecularly targeted therapy was prescribed to 699/2579 patients (27%), and only 163 patients (6%) received at least one target medication based on profiling. Of the 182 implemented lines of therapy based on CGP, partial response was observed in 23 (13 %) patients. At the same time, the full response was observed only in 0.9% from the total cohort [15].

The only multicenter randomized study SHIVA, phase 2 [16], included only patients with disseminated cancer, obstinate to conventional therapy, in which changes were observed in one of the three molecular pathways (hormone receptors, PI3K/AKT/mTOR, RAF/MEK); a total of 11 medications were available. The median PFS was 2.3 months in the experiment group (n=99) vs. 2.0 in the control group (n=96) (HR 0.88, 95% CI 0.65-1.19, p=0.41).

The NCI MATCH (Molecular Analysis for Therapy of Choice) trial [17] included over 40 arms, matching the number of molecular alterations based on the results of profiling using extended panels. The partial response rate (PRR) in the majority of arms was not over 10%, however, 7/27 (25.9%) sub-trials of NCI-MATCH that ended, were positive.

The results of our study are comparable with global data. They confirm the importance of application of CGP in clinical practice to improve results of treatment of patients with disseminated solid tumors. Successful performance of CGP and use of its results for the prescription of MTT assist identification of clinically significant genetic alterations, which fosters customization of therapeutic approaches.

The following turned out to be the predictors of successful performance of CGP: lower number of preceding therapy lines, lower number of revisions of biomaterial, and availability of sufficient amount of tumor tissue for the analysis. These factors require special attention when selecting the patients for the study.

Although no statistically significant differences in overall survival were found (p=0.097), some cases of extraordinary response were registered. They emphasize the potential of MTT in the achievement of positive outcomes of treatment in individual patients.

CONCLUSION

The obtained data complement the necessity of further study of factors influencing efficiency and availability of CGP, as well as implementation of new molecularly targeted medications in the clinical practices. This may help to expand the range of therapeutic options for patients with poor prognosis.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов***. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Shilo P.S.: development of the research concept, performance of the research, data collection, statistical calculations, preparation, creation and design of the manuscript. Makarkina M.L.: performance of the research, data collection, manuscript editing. Zakharenko A.A.: development of the research concept, manuscript editing, management. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Шило П.С. – разработка концепции исследования, непосредственное проведение исследования, сбор данных, статистические расчеты, подготовка, создание и оформление рукописи. Макаркина М.Л. – непосредственное проведение исследования, сбор данных, редакция рукописи. Захаренко А.А. – разработка концепции исследования, редакция рукописи, руководство. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.

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