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Awareness and obscurity: demystifying genomic profiling in real-world practice for the members of the Turkish Society of Medical Oncology (TSMO)

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Abstract. – OBJECTIVE: Molecular testing in oncology practice is increasingly being used to offer more relevant therapies to cancer patients. Our study aims to determine the real-world impact of routine incorporation of molecular testing among the Turkish Oncology community across all types of cancer and identify gaps for the first time.

SUBJECTS AND METHODS: This research was conducted in Turkey among medical oncologists from different backgrounds. The survey attendance was entirely voluntary. A questionnaire with twelve items (multiple choice +/- closed-ended) was utilized in this study to assess the effect of molecular tests in real clinical situations.

RESULTS: 102 oncologists with various levels of experience participated in this study. Most of the respondents (97%) reported successful implementation of molecular testing. About 10% of the participating oncologists said they preferred genetic tests at the early stages of cancer, compared to the majority who preferred genetic tests at the terminal stage. Molecular tests are often performed in separate locations and 47% of the oncologists were using a targeted panel specific to the type of malignancy.

CONCLUSIONS: Several informational difficulties must be resolved in order to have early personalized therapy as the standard treatment. We need accessible, comprehensive, and regularly updated databases to compare genetic profiling and its therapeutic implications. We also need to continue educating patients and physicians.

Key Words:

Next-generation sequencing, Evidence-based medicine, Precision medicine.

Introduction

The knowledge we have acquired about the genome has led to many new questions and has proven that molecular testing can be used to identify the variables that influence the occurrence of diseases being the best course of action for managing such disorders[1]. The use of Next Generation Sequencing (NGS) to manage routine cancer care has expanded and genomic studies[2,3] have increased among patients with different types of cancer.

Precision medicine is a rapidly evolving field that aims to understand the biological effects and clinical significance of patient variants and genomic profiles while considering individual variability in environment and lifestyle, also reducing the risk to not receive appropriate treatment[4-6]. Data from many sources including omics technologies are used in precision oncology research[7].

Understanding genetic differences within or between individuals revealed tumor heterogeneity and complicated the execution of conventional clinical trials[8]. International studies[9-11] have been carried out to characterize the cancer genome. A physician needs to assess the patient's molecular profile to apply the relevant treatment using the data gathered from these new technologies.

Defining treatment options based on data is important; reporting recommendations, improving clinical outcomes and standardizing terminology used in precision cancer medicine make it easier to assess genomic data. Experts from various groups have met, and database studies[9-12] have been launched to establish a classification system based on the data that is already accessible. One of the programs that answer these demands is The European Society for Medical Oncology Scale for Clinical Actionability of Molecular Targets (ESCAT), genomic mutations were graded as tier I-V for use in clinical practice[7].

Tier I: When the target and a specific molecular alteration suitable for routine use is confirmed, a specific treatment is recommended.

Tier II: Research that is most likely to find a patient group that benefits from a specific treatment, but for which more data is required.

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Tier III: Clinical benefit that has already been gained for associated molecular targets or in other types of tumors.

Tier IV: Actionable preclinical information.

Tier V: Demonstration of pertinent antitumor activity that does not produce a clinically noticeable effect when used alone but supports the development of co-targeting strategies.

In addition, tier X has shown lacking actionable evidence.

The Oncology Knowledge Base (OncoKB, available at: https://www.oncokb.org) is another standardization-focused database that contains information about cancer mutations used by oncologists in clinical decision-making. A group of medical professionals and cancer biologists supervise it, review and audit the clinical guidelines. Based on US Food and Drug Administration (FDA) and suggestions from disease-focused expert groups and scientific literature, potential treatments are described in detail with data such as the consequences of a specific molecular change on the drug response[13-16]. The level of evidence that a specific molecular alteration is associated with drug response categorized the potential treatment effects[17].

Level 1 contains genes for which specific variations have been recognized by the FDA as predictors of response to an FDA-approved treatment in a specific disease.

Level 2A comprises alterations, while not FDA-recognized markers are still thought to be standard care predictive tests of response to an FDA-approved treatment in specific types of cancer.

Level 2B comprises alterations that are standard predictive markers of treatment sensitivity in other tumor types but for which there are either insufficient or negative data in the tumor in consideration.

Level 3A comprises mutations that are potential predictive markers of treatment response based on the use of investigational drugs that have not yet received FDA approval for any indication or off-label usage of FDA-approved pharmaceuticals. Physicians would view the use of the FDA-approved drug in this situation as investigational because the data for the former does not support the predictive value of the alteration enough to call for a change in accepted clinical practice. The mutation-drug relations are categorized as level 3B in all other tumor types and only relate to types of tumors in which clinical activity has been documented.

Level 4 alterations are potential predictive markers of response to FDA-approved or investigational therapeutics based on laboratory results and the lack of clear clinical data to support them.

Despite guidelines, the uptake of molecular testing and Comprehensive Genomic Profiling (CGP) in the community has not been uniform, and the general impact of molecular oncology on outcomes is still unclear. There must be more research done about the reasons why doctors recommend molecular testing, how they use them, and their educational requirements. There is any study that identifies the gaps in the community. The barriers still need to be diagnosed to overcome awareness issues and confusion about test strategies and decision-making guidelines such as ESCAT *vs.* OncoKB. Surveys can be utilized for this purpose to have thorough and extensive evaluation.

Subjects and Methods

We conducted this study among members of Turkish Society of Medical Oncologists (TSMO). The survey was carried out voluntarily and was sent to all members; a total of 450 oncologists and among them, 102 oncologists participated. While the most experienced oncologist has 36 years of experience, the least senior one has one year of experience. More than 60% of the participants had 1-10 years of experience (41% had 1-5 years, and 20% had 5-10 years). Community-based questionnaire (including 12 questions) shown in the **Supplementary File 1** is designed to analyze the real-world clinical practice of molecular testing including the CGP.

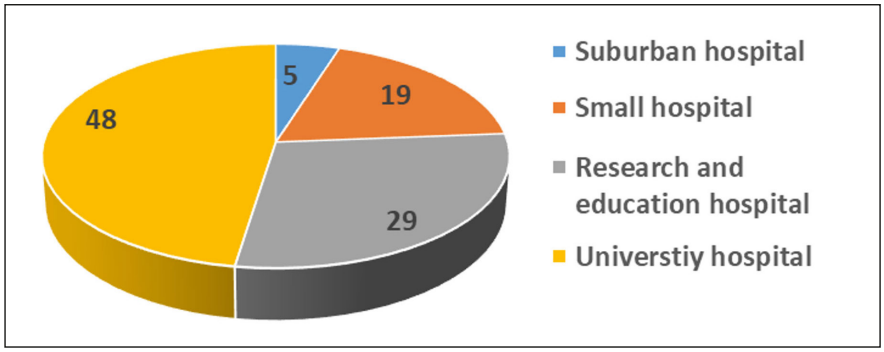
Statistical Analysis

SPSS v. 22 (Statistical Package for the Social Sciences; IBM Corp., Armonk, NY, USA) program was used in the analysis of the data. Descriptive data are presented as numbers and percentages. Inferential analyzes were not performed.

Results

A total of 102 oncologists participated in the survey. Forty-eight (47%) of the oncologists who participated in the survey work in university hospitals, followed by twenty-nine (28%) in training and research hospitals, nineteen (18%) in other private clinics, and five (4%) in public hospitals (Figure 1).

Figure 1. Hospital distribution.



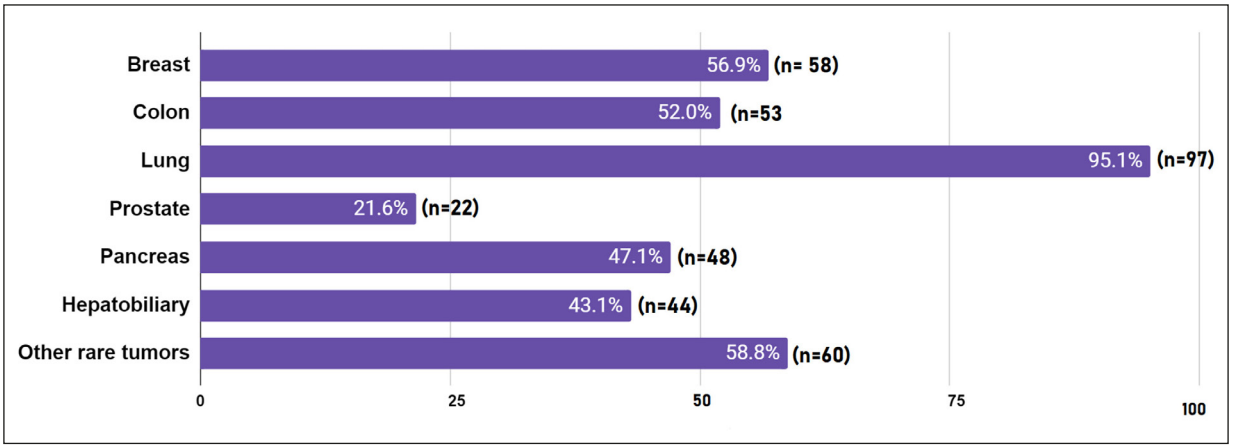


Figure 2. Samples with different cancer types.

Patient samples were from different types of cancer, as seen in Figure 2.

Key points of the results but not only limited to the abstract; most of the respondents (97%) reported successful implementation of molecular testing and most of the patients chosen had an advanced stage of cancer (90%). However, the main gap in using molecular testing seems to be the sending-out process (61%). The testing results have a clinical benefit on the treatment decisions (96%). However, the most common reason for re-testing (58%) might be not receiving an interpreted report (44%). Even though 56% of the test results were clinically interpreted, the non-homogenized criteria used (40% ESCAT and 25% OncoKB) was another gap revealed (Figure 3).

Oncologists' expertise lasted at least a year and a maximum of 36 years. Forty-two oncologists (41%) with experience between 1 and 5 years participated, as did eighteen oncologists (17%) with experience in oncology over 15 years, twenty-one (20%) with experience between 5 and 10 years, and eighteen oncologists (17%) with experience between 10 and 15 years. Forty-one oncologists (40%) said they evaluated their genetic tests in the same hospital, compared to sixty-one oncologists (59%) who said they transmitted the results to an outside facility. Twenty-eight oncologists (or 27% of the group) responded "I don't know" regarding the facility's accreditation and licensure (Figure 4).

Discussion

Genomic profiling is not only a diagnostic test, but it also has a therapeutic impact on the management of cancer patients, so it forms the basis of precision medicine[18]. These tests can be lifesaving when used efficiently. The efficacy of precision medicine in improving and/or replacing conventional cytotoxic chemotherapy has increased. In different clinics, a huge percentage of physicians express trust issues in their capacity to propose the appropriate treatment based on genomic data[19]. Oncologists who are participating in our survey also worked in different centers and the majority conducted tests at another institution.

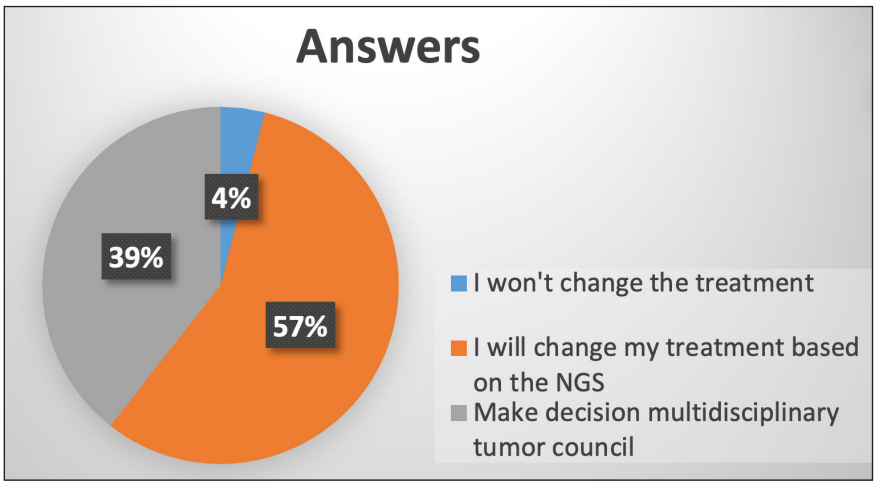


Figure 3. Deciding treatment for patients who are categorized as ESCAT 3-4 or OncoKB 3-4.

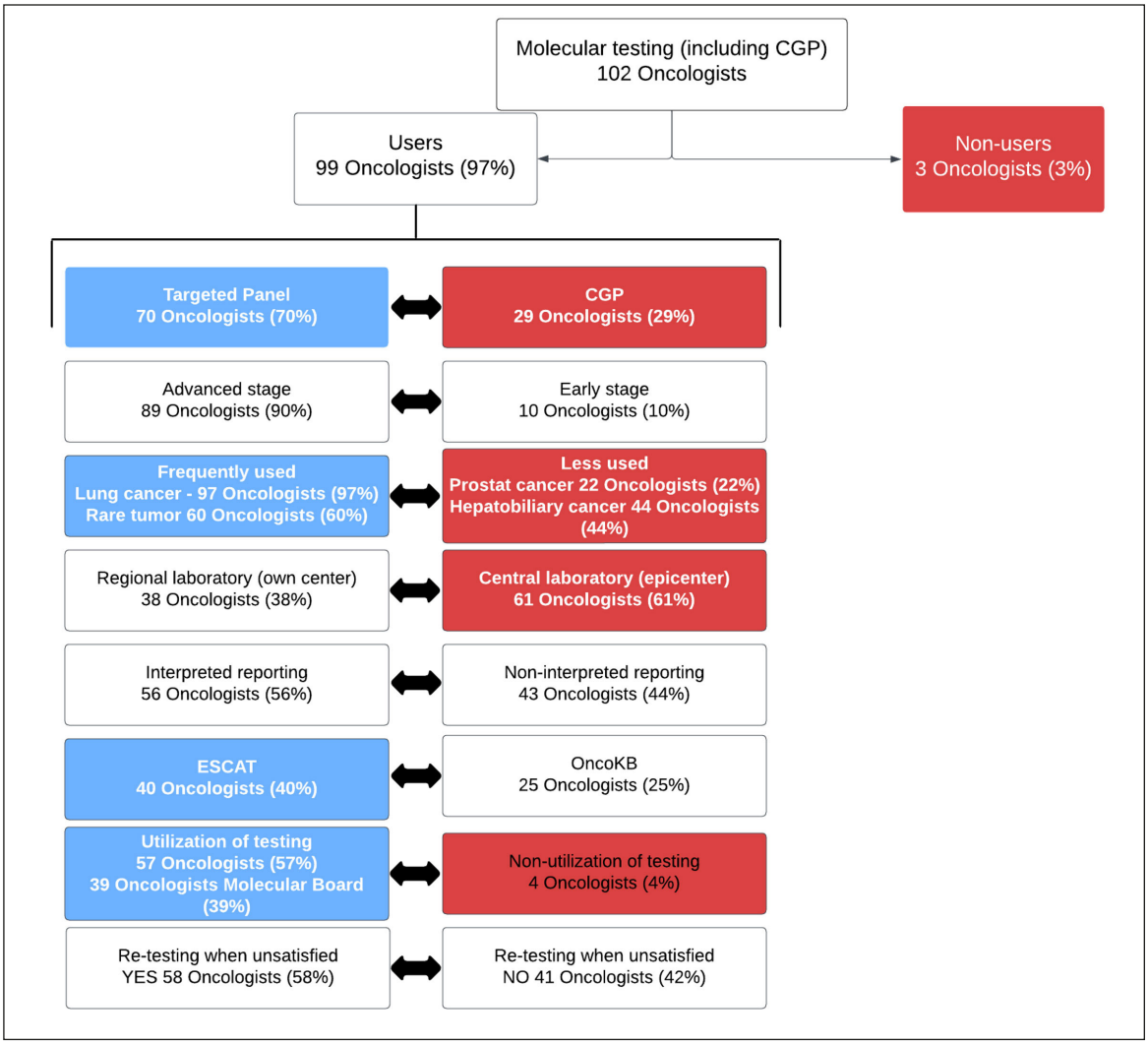


Figure 4. Additional survey-related statistics with results.

The FDA has currently approved some targeted agents, which are used clinically to treat various cancers[5,20]. Prospective clinical studies provide the clearest degree of evidence for determining if a genetic mutation qualifies a driver as a legitimate treatment target. Therefore, more oncologists should have access to these tests on time and be equipped to evaluate correctly[21]. Optimizing patient matching to early-stage clinical trials is of great interest, finding the best approach that provides data in ways that are clinically helpful for oncologists. However, there are still several obstacles to the widespread adoption of precision oncology, including the need for enhanced therapeutic procedures, the inability to accurately obtain and interpret high-quality molecular and clinical outcomes data, a lack of knowledge regarding gene alterations, limited access to genomic testing and questionable, inconsistent reimbursement policies for genomic tests and physician expertise in the understanding of molecular information[22,23].

There are some unanswered questions[24], for instance what should be documented, how to format the assessment, and whether and how to alert providers of new clinical evidence. Currently, molecular tests are under the control of the private sector, and this poses another problem for developing countries such as Turkey, especially as a country with a high population and high ratio of cancer patients. We observed that physicians' expectations for using the test and their perspectives on revealing genetic information of different values have changed. Dissemination of these tests, ensuring their accessibility, and providing the right treatment to suitable patients at the right time would help ESCAT and OncoKB create a positive social impact.

Nearly half of the participating oncologists reported using narrow panels tailored to the type of malignancy possibly due to the high costs of these tests in Turkey. Comparing genotype and curative effect across large cancer cell line panels can help identify genomic associations with therapeutic responsiveness[25]. Including all these details in a report might be challenging as gene panels are larger. All crucial data should be on the first pages of the report and formatted in a conspicuous way to increase the likelihood that it will be seen and understood by the treating physician, as data on pages 2 or beyond stand a strong probability of being overlooked by the physician[26].

The overwhelming majority of oncologists said they prefer to have genetic testing done when the disease has progressed. However, molecular testing should not just be ordered for patients with severe, late stage who have used all available treatments; instead, clinicians should be urged to request the testing as early as possible during the patient's care[26]. Sometimes getting the results takes plenty of time. Genomic profiling results in approximately 4-6 weeks in Turkey, so some patients do not live long enough to benefit from the test results.

Lung cancer was the disease that the testing was requested most often, with "Rare Diseases" as the response for the second most often listed disease. Given that genomic testing involves multiple genes, prospective clinical studies will not be powerful enough to determine the clinical importance of rare variations. To assess the clinical relevance of these mutations clinicians still require guidance[27].

OncoKB and ESCAT, a publicly available, knowledge library of somatic variations that classifies each variant with a level of evidence, were evaluated for the physician assessment of genomic actionability[28]. Although there are leading databases of information supported by evidence, OnkoKB and ESCAT were not sought in the reports, according to nearly half of the participating oncologists[29]. Compared with some other research, it has been found that a substantial percentage of physicians are unaware of the guidelines connected to genetic testing and are unable to consider these recommendations when making testing decisions[30-33]. On the positive side, molecular screening is important to physicians in Turkey, more than half of the physicians reported they changed treatment according to the NGS.

From 1 to 4 levels are presented for evidence-based recommendations in precision oncology[28]. There is typically consensus at levels 1 and 2 for participating physicians, but there is insufficient data to support the benefits of level 3 and level 4 interventions (Figure 3). To eliminate unnecessary therapies, reduce side effects, and enhance patient living conditions, would be helpful to consult a molecular multidisciplinary council that includes experienced oncologists, bioinformatics professionals, molecular biologists, and pathologists.

In some circumstances, experts from specific professions, like surgeons or others, should be consulted for additional insight[34,35].

With this study, we tried to increase awareness and identify and close gaps. The purpose of this project, which is the first in Turkey, is to increase

awareness of molecular testing throughout the nation to identify the suitable patient, the best testing approach for clinical benefit, and its harmonization with OncoKB standards. As mentioned in the methodology part, the high participation of the young oncologists was remarkable. Also, there is an opportunity to change the perspective of more experienced physicians on genomic profiling. This may also be due to the difficulty in the accessibility of genomic profiling tests in all developing countries like Turkey, where there are some common deep psycho-socioeconomic reasons. As a result, awareness will make a great difference in the use of these tests in a suitable patient, at right time, and in the elimination of incorrect treatments. This study can be a simple but important guide in this matter.

Conclusions

Molecular diagnostics is referred to as the identification of genomic changes to facilitate diagnosis and treatment - it monitors both susceptibility and resistance. Thus, this kind of contribution in the medical oncology area in turn becomes vital for the accurate provision of cancer patient care. We believe standardizing the process, educating oncologists, and enabling access to genomic profiling will help doctors save more lives, which is the end goal of several databases such as OncoKB.

The database's role rise-up as pivotal after the high-throughput methods such as NGS in clinical practice due to the cumulative knowledge-based effect of providing reliable and quick analysis of ever-more complicated variants and classifications. To solve these issues, not only a multidisciplinary but also an interdisciplinary team of decision-making is the only reliable precision oncology methodology including medical oncologists, oncological surgeons, pathologists, medical geneticists, molecular geneticists, and bioinformaticians.

More than these, there is still a need to perform comprehensive genomic profiling for lung or rare cancers as our study showed the most used indication. The other most important conclusion is the need for ongoing training programs including molecular testing algorithms and the use of databases for both clinical and patient sides. However, several informational issues must be resolved for genetically individualized medicine to become our most common reality in oncology practice in Turkey.

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Ethics Approval
The study was approved by Ethical Committee for Non-Interventional Studies of the Faculty of Medicine, Cukurova University, Adana, Türkiye (June 3rd, 2022 and Decree No.:123).

Informed Consent
All participants signed informed consent for inclusion.

Availability of Data and Materials
The data of the study are available from the first and corresponding author.

Conflict of Interest
There is no conflict of interest in this study.

Authors' Contributions
Ertugrul Bayram, Berksoy Sahin; conception and design of the study, acquisition of data, analysis, and interpretation of data; drafting the article, making critical revisions.

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