THE WORKSHOP REPORT: CHALLENGES & OPPURTUNITIES IN MOLECULAR BIOMARKER-BASED PERSONALIZED PRECISION MEDICINE IN THE TREATMENT OF CANCER

TURKISH ASSOCIATION FOR CANCER RESEARCH AND CONTROL

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FOREWORD

Recently, significant progress has been observed in the diagnosis and treatment of cancer; particularly, the advances in molecular and genetic techniques and their introduction to clinical practice in addition to technological advances in pharmacological industry that allowed manufacturing high technology drugs for relevant molecular targets in cancer treatment have resulted and continue to result in significant leaps forward in the treatment of cancer. Such dazzling progress requires a significant perception change also in the approach to cancer patients. This is important not only for the patient and the physician who treat cancer patient, but also for healthcare providers as well as regulatory agencies and relevant related organizations. The reason for behind this is the transition from a classification and treatment approach based only on the originating organ and histological structure of cancer to a more complex period of molecular and genetic classification, typing and subtyping, all of which have become more prominent in terms of treatment. This has led to the need to determine the standards for the rapidly evolving field of molecular pathology as well as the need to ensure optimal access to these diagnostic and therapeutic treatment modalities for both the patient and the physician. Enabling patient access to innovative treatments or, with the vernacular of the day, allowing the patient to benefit from molecular biomarker-based personalized targeted medicine is a vital necessity which cannot be delayed or ignored. This is of special interest not only for medical oncologists, but also for all specialties that provide solutions to cancer patients. Within this context, in this workshop, we worked with experts in this field to investigate the opportunities and issues regarding molecular biomarker-based personalized targeted treatments in current cancer environment in order to evaluate the topic in terms of its all aspects which concern the patient directly, and I, Prof. Dr. Suayib Yalcin (Hacettepe University Cancer Institute, Department of Medical Oncology) on behalf of the Turkish Association for Cancer Research and Control, and Prof. Dr. Faysal Dane (Acibadem Altunizade Hospital, Department of Medical Oncology), Prof. Dr. Emel Cabi Unal (Ankara University Faculty of Medicine, Department of Pediatric Hematology and Oncology), Prof. Dr. Nalan Akyurek (Gazi University Faculty of Medicine, Department of Medical Pathology), Prof. Dr. Nuriye Yildirim Ozdemir (Gazi University Faculty of Medicine, Department of Medical Oncology), Prof. Dr. Mehmet Ali Nahit Sendur (Ankara Yildirim Beyazit University Faculty of Medicine, Ankara City Hospital, Medical Oncology Clinic), Prof. Dr. Toker Erguder (WHO Turkey Office), Assoc. Prof. Dr. Atil Bisgin (Cukurova University, AGENTEM (Adana Genetic Diseases Diagnosis and Treatment Center) and Faculty of Medicine, Department of Medical Genetics), Assoc. Prof. Dr. Hilmi Kodaz (Acibadem Eskisehir Hospital, Department of Medical Oncology), Specialist Dr. Hakan Taban (Hacettepe University Cancer Institute, Department of Medical Oncology) and MSc. Pharm. Burcum Uzunoglu (Rx Corporate Communications) collectively prepared this report to present it to the public and relevant authorities and decision makers. I would like to thank all our workshop attendees for their valuable contributions and efforts, Rx Corporate Communications, particularly MSc. Pharm. Burcum Uzunoglu, for their meticulous work and support, and Assoc. Prof. Dr. Ali Muhittin Tasdogan (Member of Parliament, Grand National Assembly of Turkey Health, Family, Labor and Social Affairs Commission) for their kind & valuable support in the workshop.

Kind regards,

Prof. Dr. Suayib Yalcin
President of Turkish Association for Cancer Research and Control

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TABLE OF CONTENTS

FIGURES

TABLES

1. The Burden of Cancer in World and in Turkey

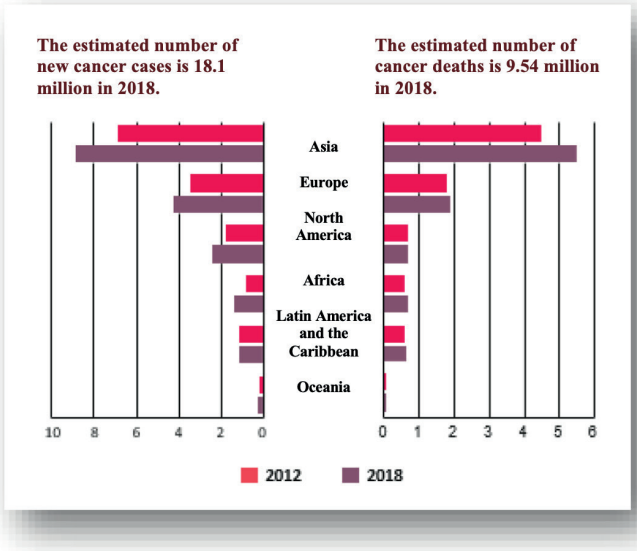
Cancer is a major global issue and the second leading cause of death worldwide. While the number of global cancer deaths was 8.24 million individuals in 2012, this figure increased to 9.54 million individuals in 2018. Nearly one in six deaths is due to cancer.[1] In 2018, Asia had the highest number of cancer deaths with around 5.5 million deaths, followed by Europe with 1.9 million deaths.

In our country, the number of annual new cancer cases was estimated as 233.834 in 2020, while the number of cancer deaths was estimated as 126.335. In 2018, these figures were estimated as 210.537 and 116.710, respectively. Turkey is a country with increasing population. While our population was 81.916.866 in 2018, it increased to 84.339.067 by 2020 and continues to increase. As a result of this increase, the annual number of newly diagnosed cancer patients and cancer deaths also tend to increase.

On the other hand, a similar increase in the burden of cancer is noted worldwide; e.g. while 14.1 million individuals were diagnosed with cancer in 2012 worldwide, this figure reached 18.1 million in 2018. The incidence of cancer and regional distribution of cancer deaths are shown in Figure 1. Cancer constitutes an enormous burden on patients, their families, and the society, and remains a major threat to public health worldwide.

As the second leading cause of death globally, it was responsible for 8.8 million deaths in 2015. Nearly one in six deaths is due to cancer.[2] The number of new cancer cases is expected to rise by about 70% over the next two decades.[3] According to the Globocan 2020 statistics, the annual number of cancer cases is 19.3 million worldwide and the number of annual cancer deaths was predicted as approximately 10 million, excluding nonmelanoma skin cancers.

Figure 1. Cancer deaths and new cases in 2012 and 2018 by different regions (in millions)[1]



Over the last few years, there has been significant success in the diagnosis and treatment of cancer, leading to a significant increase in survival rates and the quality of life of patients. It is estimated that there are currently 33 million people living with cancer worldwide. Approximately 73 percent of survival gains are attributable to the increased treatment success with new drugs.

For instance, in 1975, less than half of the patients diagnosed with cancer could survive five years. Today, two out of three patients diagnosed with cancer survive at least five years.[4] In the USA alone, 4.5 million additional patients are expected to achieve survival from cancer by 2026 as a result of the advances in pharmaceutical research and newly developed drugs.[5]

Cancer is not only a very burdensome disease for patients and their family members, but also constitutes an economic burden on the individual, the caregivers, and all stakeholders of the healthcare system. In 2010, cancer caused total costs of approximately US$1.16 trillion worldwide and €126 billion in the European Union.[6,7] In Germany alone, cancer leads to annual costs of €35 billion. This figure corresponds to 1.48 percent of Germany's GDP.6 A similar situation may be the case in our country as well, considering the similarities in size and population. On the other hand, 40 percent of direct and indirect economic costs of cancer result from the healthcare services administered to the patient. The remaining 60 percent is caused by workforce loss of patients and the loss of productivity of family members who need to discontinue working to care for the patients.[8]

An important driver of increased costs related to cancer is the loss arising from early deaths of the patients or not being able to continue their work life. This loss is important primarily for the individual, secondarily for their family and relatives and finally, for the society. For example, 67 percent of patients who had full-time employment when diagnosed with cancer either stopped working or reduced their work hours. More than 25 percent of caregivers had to make long-term employment changes. Loss of productivity due to early mortality related to cancer is enormously high, and according to 2018 data, of the total cancer disease burden of €199 billion in the European Union, €103 billion were used as healthcare expenses for the management of cancer disease, while the cost caused by total productivity loss was €70 billion.[9] The €50 billion part of this cost is related to the productivity loss caused by premature mortality.

The other socioeconomic losses are attributed to family members who discontinue working to care for the patient. In Europe, free-of-charge care of three billion hours was provided for patients' family members and friends, which corresponds to a total of €20 billion.[9]

Similarly, in our country, those diagnosed with cancer generally discontinue working, obtain long-term incapacity report, or retire early. Each of the caregivers are allowed to take accompaniment leave for up to 6 months.

2. Barriers to Access Innovative Oncology Drugs in the Developing Countries

Despite their relatively larger share of population, less developed countries account for 57 percent of cancer cases and 65 percent of cancer deaths worldwide.[10] But cancer is often still neglected as a disease due to national healthcare strategies tediously focusing on communicable or metabolic diseases. In those countries, the situation is very tense for cancer patients and their families.

An urgent need exists for an holistic national cancer policy that includes, awareness raising activities in public, initiatives to increase the number of experts in the oncology area, enhancement in the early diagnosis and delivery of the adequate treatment, and in the treatment outcomes, especially with a focus on access to innovative oncology drugs.
Access delays are more prevalent in less developed countries. Below is a summary of healthcare system-derived barriers that prevent oncology patients from accessing timely appropriate treatment:

Delayed diagnosis and limited number of cancer experts

Poor cancer screening systems are a major challenge in low- and middle-income countries. Due to late diagnosis, the management of cancer treatment becomes difficult. At a late disease stage, treatment options are more expensive and less effective in terms of survival rates. Furthermore, most countries only have a limited number of oncologists or specialized cancer centers, or they might be out of reach for the patients in rural areas. Hence, the level of accessibility for diagnosis and adequate treatment is difficult. Additionally, these countries do not collect enough data (cancer types, mortality rates) and need to enhance their systems to collect health data to make decisions for the innovative treatments.

Delayed and/or limited approval to innovative treatments

Rapid approval from regulatory & reimbursement agencies and decision makers is a major milestone on the path to extend survival and improve the lives of patients, especially those with advanced cancer who have only limited treatment options. In developing countries, it is important that the decision maker have clear guidelines for the approval pathway. Also, it is critical for such bodies to consider issues of technical expertise & know-how. (e.g. regarding international standards, pharmacoeconomics).

A growing discrepancy in the quality of cancer care

The current status quo-oriented healthcare policies in low- and middle-income countries mean that these countries cannot keep pace with the rapid advances in medical science and new cancer treatments. As a result, huge discrepancies arise in the quality of cancer care. This gap grows constantly and will continue to grow unless these countries try to implement structural political changes in their healthcare systems. More than half of cancer drug expenditures across emerging pharma markets are for medicines that were first launched more than twenty years ago.[11]

Cost of cancer treatment

In any debate about the escalating costs of innovative cancer drugs, one should look at the costs eliminated with the introduction of innovative drugs. This cost saving may be achieved either by preventing the occurrence or worsening of a chronic disease. In general, as the disease becomes more severe, the associated costs to the healthcare system will be higher due to the costs for inpatient visits, outpatient treatments, and hospitalizations.

In the face of the rising numbers of cancer patients due to aging societies, it is important to lower inpatient costs per case as they constitute a certain ratio of all cancer-related costs. Highly effective cancer drugs can reduce such costs by minimizing the severity of a disease. Enabling access to curative treatments, avoiding severe and impairing interventions, or even curing patients, results with lowering hospitalization rates and other overall treatment costs while providing a sustainable healthcare system and improved quality of life values for the patients.

3. Recommendations to Reduce the Burden of Cancer on Society

Cancer is a complex disease with more than 200 different histological types. Therefore, oncologists should have access to the utmost number of treatment options as far as possible to identify the treatments that serve best for patients' needs. Despite the different factors contributing to cancer survival rates, countries that further utilize new cancer treatments observe better outcomes in the clinical findings and quality of life of patients affected by cancer. However, there are significant inequalities in patient access to cancer drugs across different countries and regions. Developed/high-income countries (HICs) are usually more rapid adopters of new treatments than less developed/low-to-middle income countries (LMICs). [12] Limited access results from manufacturers not applying for regulatory approval, delays or refusals of the access approvals, or manufacturers awaiting the results of reimbursement negotiations prior to launching the drug in the relevant country.

A major issue in the healthcare system is its failure to be sufficiently prepared for innovations in oncology. Even in developed countries, it is becoming increasingly challenging for established healthcare systems to absorb and digest a rapidly changing technology landscape ranging from combination therapies and immunotherapy to personalized targeted oncology treatments and its related diagnostics. This situation applies for regulatory approval, pricing, and reimbursement procedures as well as implications in clinical practice.

The risk to develop cancer increases with age. With the average life expectancy continuously increasing, societies are growing and more people are being impacted by cancer. However, the societal burden of cancer is not increasing only due to the growth and aging of the population. Lifestyle factors, such as smoking and an increased body mass index (BMI) which may be linked to the increasing wealth of most countries also play important roles in this regard.[13] Between 30–50 percent of cancers can be prevented by avoiding risk factors and implementing the currently available evidence-based prevention strategies.[1]

Additionally, oncology-specific access initiatives shall be implemented in developing countries. Developing a new reimbursement model and efficiently analyzing the clinical benefits provided to the patients within a sustainable healthcare budget may increase access to oncology treatments in such countries, contributing positively to patients' health outcomes.

There are many policy recommendations that may help to improve access to innovative drugs for patients: Investing in early diagnosis and increasing the number of specialized cancer centers, building effective cancer databases to better understand the patients burdens and needs for different cancer types, reducing access delays and barriers for patients, and establishing dedicated cancer care funds within the national healthcare budget, are possible measures to lessen the barriers of access to innovative oncology treatments in the developing countries.

Early diagnosis and optimal management of cancer may also assist in the alleviation of the overall burden. Cancers have a higher chance of being cured if diagnosed early and treated adequately. Although more people are diagnosed with cancer, innovative personalized targeted treatments along with improved screenings and earlier diagnosis help patients to live longer and with a better quality of life.

In recent years, thanks to achieving a better understanding of the disease biology, the translational research in this field, and newly developed drugs, certain types of cancer such as breast, prostate, colon, ovarian and lung cancer have become a chronic disease. Established cancer databases have enabled a clear understanding of healthcare policy recommendations that should be implemented for different types of cancer. With the implementation of these policy recommendations, patients would be able to maintain their daily life, continue their work life, play an active role in the society and economy through access to timely and efficient treatment leading to improved survival rates. Thereby, the elderly patients would live longer, in a more active & fulfilling live.

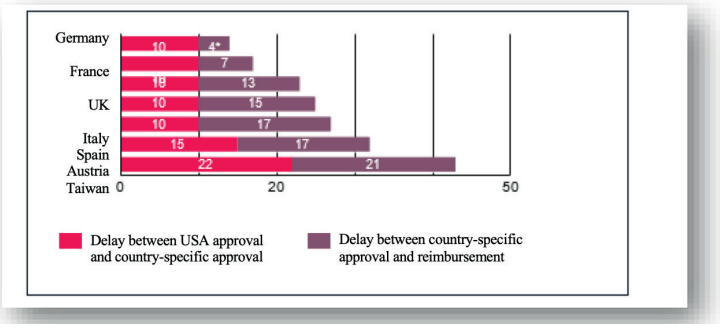
United States of America has prioritized evaluations of innovative drugs by increasing private and public investments in drug discovery and widening access to diagnostic tests that helps clinicians enable appropriate treatments to their patients. The number of new-generation personalized medicine options has risen significantly, mostly in the USA. Since 2006, the USA Food and Drug Administration (FDA) has approved 31 personalized medicine cancer drugs with a total of 38 indications.[14] Unfortunately, accessibility to cancer drugs is not at the same level in the worldwide. There are significant inequalities in patient access to cancer drugs across different countries. Some countries are more rapid adopters of new treatments than other countries. Patients in some countries face long delays in gaining access to effective new cancer drugs. This is mainly caused by regulatory, pricing and reimbursement approval processes.

Innovative novel treatments may help tackle the global burden of cancer. To ensure that future medical innovation continues to bring new hope to patients in the form of effective treatments, governments should recognize the substantial benefit from innovative therapies and work to improve their healthcare systems to ensure a pro-innovative regulatory, pricing, and reimbursement ecosystem in order to generate access for the adequate treatment to the right patient at the right time.

It is inevitable that the pack prices of innovative drugs are higher compared to older drugs. However, it may be a mistake to focus on only the issue of the price while establishing policies and pricing for innovative drugs. The values brought by these drugs for patients and societies should also be considered while assessing the effect of such treatments on the long-term sustainability of healthcare budgets. Naturally, drug prices and the effect of these novel drugs on the national healthcare system cause concerns particularly in this period during which there is an increase in pioneer novel treatments targeting rare cancers. As a matter of fact, fears that the prevalent use of such new cancer drugs may threaten the financial stability of economies and present a threat for the future have not come true entirely. These drugs are also a major part of the economy's increasing production capacity and may also help reduce costs in other parts of the healthcare system, such as inpatient treatments, length of stay in emergency department, hospital visits, diagnostic procedures, or even other (concomitant) medications while contributing to direct and indirect economic growth. Therefore, innovative cancer drugs may contribute to an optimized reallocation of finances in healthcare budgets, thus increasing the overall efficiency of a healthcare system.

The lack of more efficient innovative drugs may in fact pose a larger threat against national healthcare systems in the future since it leads to multifaceted increases in the costs of chronic diseases in the aging society. On the other hand, enhancing access to cancer treatments does not necessitate significant increases in healthcare budgets since the disease already exists and receives diagnosis and treatment anywise. A rational reallocation of healthcare funds and faster pricing and reimbursement processes would be sufficient to utilize more efficient innovative treatments for these patients. However, even the European countries which demonstrate similar levels of cancer care expenditures use cancer drugs very differently. The reason for this is the fact that Health Technology Assessment (HTA) decisions are not standardized. Consequently, patient access and time to access drugs differ considerably within the European Union.[15]

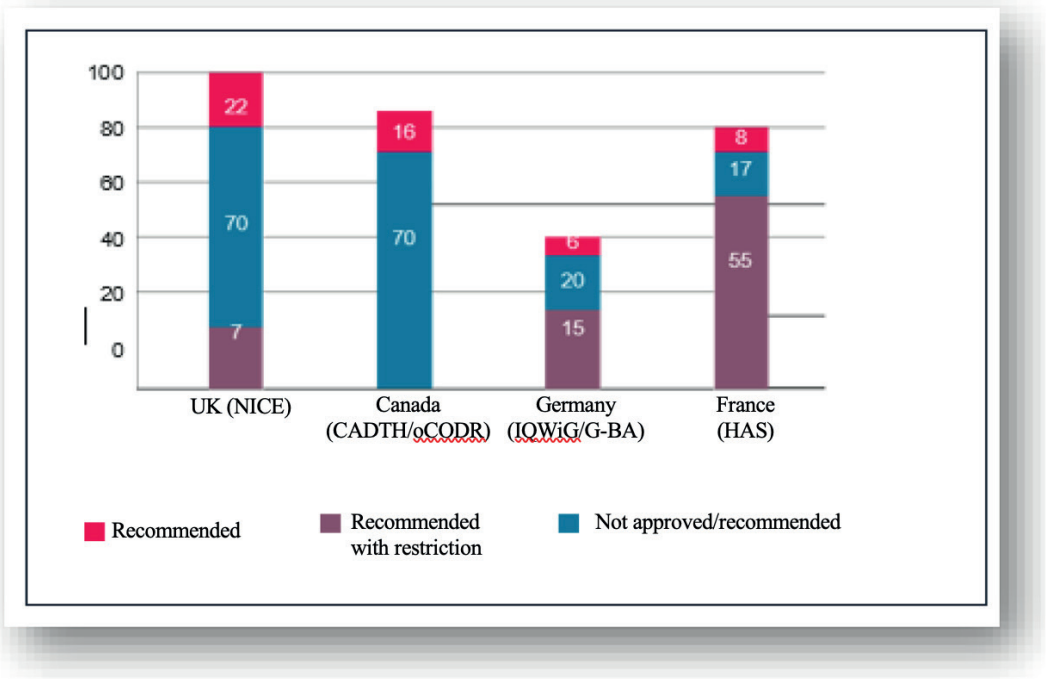
Figure 2. Average delay (in months) in the approval and reimbursement of oncology drugs in some countries compared to the USA in 2010–2014



*After EMA approval, each EU member state conducts a review of the new drugs.
According to EU Transparency Directive, a review should take no more than 120 days (4 months). (http://europa.eu/rapid/press-release_IP-12-205_en.htm)
According to IQVIA, Germany needed 3.1 months on average from EMA approval to first sales in 2017(https://www.iqvia.com/library/publications/pricing-and-market- access-outlook-2018)

Outcomes of Health Technology Assessment decisions differ across countries.[15]

Figure 3. Outcome of the Health Technology Assessment (HTA) for cancer treatments (2013-2017)



The progress in cancer treatment is based on advancements in molecular and genetic research which reveal the complex features specific to cancer and change our understanding of cancer. Now, we know much better the causes of uncontrolled growth of body cells. However, cancer is much more complex and varied than a single cancer cell and each case carries unique characteristics. Each person's genetic makeup is different. Similarly, each patient has a whole range of factors that trigger and affect cancer. In fact, the condition referred to as "cancer" comprises hundreds of different diseases. Patient care in oncology is evolving very rapidly in different dimensions and with increasing complexity.

Understanding the complexity of cancer and treating cancer patients mean accepting that there is no single cancer, as there is no single cure for cancer. Furthermore, we accept that cancer and its treatment may not end in most cases, but rather it is possible for patients to achieve remission, have prolonged survival, or improve their quality of life. This is very much supported by today's numerous innovative personalized precision treatment approaches.

While "breakthrough" innovative precision cancer drugs are being added to our ammunition each day, incremental advances seen in the field of rarer or difficult-to-treat cancers create a huge problem for patients who do not respond to current treatments. Progress in the diagnosis and treatment for some types of cancer has been frustratingly slow. The survival rates for patients who suffer from liver cancer, for example, are still very low, with fewer than 15 percent of individuals experiencing long-term survival from this type of cancer in most developed countries. Steady incremental advances in research and development are vital to positively impact the way cancer is treated. Therefore, patients need innovative drugs that may help extend their survival and improve their quality of life.

With the advances in molecular pathology, discovery of novel treatment targets and development of drugs directed at these targets, we are witnessing a transition from nonspecific, one-size-fits-all treatments for all patients to personalized, targeted and precision treatments based on molecular analysis. This is a real paradigm shift. This shift is based on the discovery of biomarkers that play an essential role in the identification of specific cancer types as well as treatment choices. Molecular pathology and genetic studies are needed to detect these biomarkers. Thus, by means of biomarkers, personalized medicine and tumor agnostic oncology treatments may be implemented, allowing patients to receive drugs with proven clinical efficacy while reducing the risk of adverse events. As soon as these innovative drugs are made accessible within the healthcare system, oncologists would be provided with additional options to maximize treatment response among their patients.

The Need to Move Towards Value-Driven Healthcare Systems in Cancer Treatment

In the context of medical science evolving rapidly and having to confront the challenge of providing high-quality healthcare for aging populations with an increasing burden of chronic disease, it is important to shift from healthcare financing and delivery systems that focus on quantity to systems that focus on the quality and value of care. As such, it is important to implement flexible, country-specific pricing arrangements, such as indication-based or outcome-based pricing agreements for innovative drugs.

Price control measures differ from country to country. Likewise, the ways these policies are implemented differ in terms of predictability, transparency, recognition of value, and the view towards long-term impacts. The implemented pricing control measures may be stratified differently along the life cycle of a given drug. When launching a new oncology treatment, a Health Technology Assessment (HTA) is the most effective instrument. This assessment sets the initial price for the new medicine. The benefits or value of pharmaceutical products are assessed in a broad variety of ways in several countries around the world. These value frameworks are usually designed to form an informative foundation for determining national healthcare priorities and allocation of healthcare funds by payers. Thus, they have a direct impact on physicians' ability to select the best treatment option.[16]

The number of Health Technology Assessments has doubled in the past five years across countries. For example, in 2017, less than half of these assessments resulted in a positive recommendation, and very few made consistent recommendations across countries. This highlights the varied thresholds and approaches in use.[17] Even within the EU, there are numerous independent healthcare systems in operation, and each Health Technology Assessment body follows its own methodologies and scientific value appraisals in assessing the value of innovative anticancer drugs. A benefit rating tailored to the country-specific context exists in each country.[16] The clinical benefit of treatments is assessed considering real-world data or if this is not possible, with surrogate endpoints. Value assessments are typically based on clinical evidence from phase 2-3 studies designed to achieve regulatory approval. One specific issue, particularly important in Health Technology Assessments in oncology, is the acceptance of the so-called "surrogate" endpoints for the overall survival (OS) endpoint in clinical trials. The analysis of overall survival (OS) not only requires long follow-up periods, but also delays the development of the drug and makes any clinical trial impossible from a methodological point of view. In some cases, the OS endpoint can only be reached after many years. Evaluating the OS of an investigational drug is often also limited for ethical reasons. This is particularly true if follow-up treatments for later stages of the disease exist and can extend the patient's survival. Health Technology Assessments (HTAs) around the globe have different views on these surrogate endpoints.

HTA is a powerful tool to assess the long run value of new medicines from different stakeholder perspectives. The pharmaceutical industry supports the use of sound evidence for informed decision-making in healthcare. Value/impact assessments should not be used to delay or restrict patient access to innovative medical products or treatments. Instead, the value of innovative drugs should be assessed under transparent, evidence-based, scientifically sound, and predictable frameworks that ensure an open dialogue with all relevant stakeholders. A holistic and patient-centered understanding of the assessment of the value of innovative pharmaceutical requires healthcare systems to make the patient's experience and patient-reported outcomes a central aspect of their value assessments. Patients and their physicians should therefore play a central role in the development of value assessment frameworks and decision-making processes. Decision makers should begin to facilitate flexible, country-specific pricing arrangements, such as indication-based and outcome-based pricing agreements for innovative drugs. Governments should ensure that any efforts to introduce a Health Technology Assessment system should take place in an open and transparent manner with all stakeholders. Governments should take experiences in other countries into account and develop appraisal methods that appropriately value innovative drugs and reflect the full value of oncology drugs for patients, providers, and caregivers.

4. The Future of Oncology Treatments: Personalized Treatment by Precision Medicine

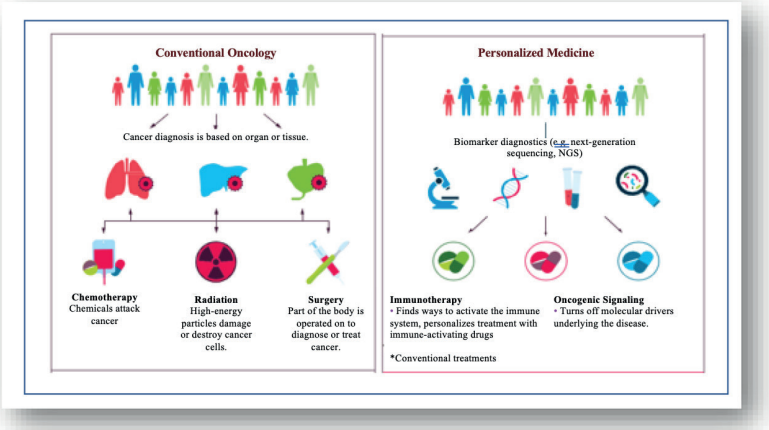
Cancer is increasingly being considered a disease of the genome. Each person's genetic material is unique, thus every patient's cancer is driven by a specific variety of factors. New advances in genomics and molecular biology have further improved our knowledge of the inner workings of cells. Scientists are now looking at the molecular level to understand what drives tumors to grow. In the past, surgeons used to operate two-thirds of all new cases of lung cancer and the remaining third of the cases were deemed inoperable. Only six percent of new cases, however, were cured with surgery. Most of the patients with colorectal cancers used to undergo surgery, but only a third of these individuals were cured overall. Although about 90 percent of women with breast cancer presented with "localized disease" –that is, cancer that had not spread– only 40 percent of the women were successfully treated with surgery and radiation. The other 50 percent already had tumor cells in their bloodstream at the time of their surgery, which meant inevitable recurrence.

In the past, surgeons used to try to improve the survival rate through radical operations. Over the last 30 years, academic and private research provided tremendous knowledge about the origin of cancer in cells as well as the ability of cancer cells to adapt to changing environments. Science leads to entirely new approaches and treatments in all fields of oncology by revealing the complex structure specific to cancer, thereby enabling a better understanding of the disease. Understanding the complexity of cancer and treating this disease means accepting that there may not be a single cause for cancer. Scientists and physicians now recognize that no two cancers are alike. Cancer occurs in countless forms, and every tumor has different biochemical or genetic background. It is therefore impossible to develop a "one-size-fits-all" treatment for cancer. Individual differences between patients (such as genes or age) influence not only the onset of disease, but also how drugs are absorbed and metabolized in the body. Abnormal changes to genes may lead to the alteration of proteins, which do most of the work in cells and are required for the structure, functioning, and regulation of the body's tissues and organs. As a result, these altered proteins drive the growth and spread of tumors. Knowing about these genomic drivers means that scientists can specifically target "oncogenic drivers" of cancer at the molecular level.

Today, most innovative cancer treatments target and destroy specific tumor cells not based on their location in human organs or tissue (i.e. lung, prostate, breast, skin, etc.) but by targeting the molecular pathways that are of vital importance for the tumor. These interventions represent a major advance compared to non-personalized cancer treatments, such as systemic, non-specific chemotherapy, hormonal treatments, or non-targeted radiation, all of which have limitations. However, efficacy differs depending on the patient and treatment. Some treatments carry a risk of serious side effects or have limited utility beyond a limited number of tumor types. Nowadays, 46 percent of oncology treatments are targeted and 73 percent of cancer drugs in development comprise personalized treatments.[18] Targeted therapies have increased survival rates drastically. While chemotherapy responses are between 30-50 percent in most cancer types, treatment-related response rates reach up to 80 percent with specific targeted treatments.

Ground breaking personalized targeted cancer treatments (also called "histology-independent" or "tumor-agnostic" treatment) block the oncogenic drivers in cells no matter where in the primary tumor is located in the body. Such progress has led to a tendency from existing treatments for larger patient groups to personalized precision treatments based on molecular analysis for smaller patient groups. Identifying oncogenic drivers at the molecular level and targeting them directly is an increasingly important area of focus in oncology research. Novel "tumor-agnostic" cancer drugs developed based on biomarkers instead of tumor location or indication represent the beginning of a new era.

Figure 4. Diagnosis and treatment algorithm for conventional oncology and personalized medicine



The aim of precision medicine is to individualize treatments considering patients' genetic makeup and other specific characteristics. Precision medicine focuses on the genetic alterations in tumors that cause cancer. Altered genes may be detected by genomic testing, which is a type of test that identifies actionable genomic alterations. It is important that high-quality gene testing becomes part of routine clinical practice so that patients may benefit from potential treatments that selectively inhibit the oncogenic drivers underlying their cancer. Studies show that both adult and pediatric patients may benefit from personalized precision treatments through the detection of actionable oncogenic alterations in cancer patients.

5. Position of Targeted Treatments in Pediatric Patients

The incidence of childhood cancers in Turkey is similar to that of high-income western countries. Childhood cancers account for 1.3 percent of all cancer cases and about 1 percent of all cancer deaths. It is 137.9 per million in the USA, 143.2 in Norway, 149.4 in Sweden, 118.2 in the UK and 131.3 in Turkey. Approximately 3000 children in our country and approximately 175 thousand children in the world are diagnosed with cancer every year.

Causes of Childhood Cancer Occurrence and Factors Increasing the Risk

Does the mother's diet during pregnancy, smoking and similar increase the risk? In response to the question, our genetic code is the first determining factor for all diseases, especially cancer. After genes, environmental factors, air pollution, tobacco products, cigarette smoke and radiation from cigarettes come. Some infectious agents increase the risk of developing cancer. For example, Hepatitis B or C virus increases the risk of liver cancer, human papilloma virus cervical cancer, head and neck cancer, Helicobacter pylori stomach cancer. Viruses such as EBV create infections when our immune system is congenitally weak or in situations that weaken our immune system. EBV-associated lymphoproliferative disease is common in children in our country. EBV is a factor that facilitates the development of cancer and especially lymphoma. There is no screening program for childhood cancers, but the success rates of treatment with early diagnosis are high.

Today, childhood cancers can be diagnosed in many pediatric oncology centers in our country and these patients can be treated at international standards. In children, leukemias, lymphomas and central nervous system tumors are seen in both sexes, respectively. Over the years, chemotherapy, radiotherapy, which have formed the components of multidisciplinary treatment approaches.

We are pleased to see that the survival rates of childhood cancers have increased in Turkey with the developments in surgery and surgery. Today, bone marrow or peripheral stem cell transplantation can be performed actively in 33 of 36 Pediatric Stem Cell and Bone Marrow transplant centers in our country, and these treatment options are used in some resistant or recurrent cancer types. Today, we see that recovery rates increase with the introduction of some targeted molecules, targeted therapies and immunotherapy agents in addition to standard programs in treatments. Ministry of Health Turkish Medicines and Medical Devices Agency - TITCK's Economic Evaluation and Drug Supply Unit approves the use of unlicensed drugs in the treatment of pediatric patients in line with scientific data. Since its establishment in 2011, this department has been rapidly evaluating the targeted treatment programs of cancer patients in the 0-18 age group with individual treatment commissions and providing support for the use of these treatments. Clinical response status of pediatric patients is monitored with 3-month feedback in approved patients.

The 5-year survival rate in all childhood cancers is around 70 percent, with the analysis of national data obtained as a result of the proper and systematic keeping of cancer records by the Turkish Pediatric Oncology Group Association - TPOG and the Turkish Pediatric Hematology Association TPHD in Turkey since 2002. This result is 80 percent in developed countries. The target is to reach 80-90%.

It should be underlined that the high success of treatment and the long life expectancy of children who have recovered from cancer make early and effective treatment, access to the best service, quality of life, monitoring of late side effects, and psychosocial approach even more important.

Measurable improvements in clinical outcomes by providing the right treatment and care at the right time, based on evidence, to the right cancer patient with personalized medicine methods in pediatric cancers.

It is possible to achieve a reduction in health care costs by providing Therefore, biomarkers and molecular individualized medicine are replacing the traditional "one-size-fits-all medicine". In the next 10 years, the treatment of pediatric cancers will move from being reactive to a proactive discipline. The essence of personalized oncology lies in the use of molecular biomarkers. For example, NTRK gene fusions in pediatric patients, especially NTRK 1 and 3 infantile fibrosarcoma, →90% (ETV6-NTRK3 fusion), 3.7-22.2 percent in papillary thyroid cancer, 1.9-33.3 percent in spitzoid neoplasia, 1.9-33.3 percent in secretory breast cancer 92 and gliomas can be detected positive between 5.3-6.3 percent, and superior treatments can be obtained with specific agents.

These landmark treatments show promising results in the clinical setting and open the door to treatment for those struggling with rare, difficult-to-treat tumors. Thanks to specific genomic testing platforms, doctors and researchers can more accurately predict which treatment strategies will be effective in which specific group of cancer patients. In this way, effective treatments with limited side effects are provided.

More regular application of validated genomic testing (molecular-based biomarkers; accompanying diagnostic tools) could help more patients benefit from more effective treatments.

6. Molecular Biomarkers and Molecular Tests in Solid Tumors

The use of molecular biomarkers in cancer treatment in addition to understanding their pathophysiology and genetics, and the development of appropriate drugs generate new fields of treatment. "Genomic profiling", which uses gene products (transcripts and proteins) and metabolites as biomarkers, constitutes the foundation for biomarker detection. As part of this approach, technologies that can detect differences at the molecular level with increasing safety and productivity are used in practice. Referring to their sensitivity, the term "precision oncology" is also used while determining treatments by means of such technologies.

Studies in oncology have gained importance particularly due to next-generation sequencing (NGS) technologies, enabling multiple-gene panels related to diseases and even implementations such as whole exome sequencing and whole genome sequencing to take part in routine oncology practice. The genomic alterations in cancer cells are stratified based on the results they induce as driver mutations (mutation types that initiate the tumor and impact progression) or passenger mutations that do not directly drive tumor formation.

Therefore, the main target of genomic profiling as part of the ongoing routine implementations in the oncology clinic is to define the driver mutations. In many cancer types, more than one driver mutation contributes to the initiation of cancer.

Although a vast number of mutation types may be seen in the tumor tissue, the most common mutations can be separated into four groups:
1- Single-nucleotide variations (SNV)
2- Insertion-deletion mutations
3- Large deletions and/or duplications
4- Chromosomal translocation-inversion

All of the aforementioned cancer-causing mutations typically emerge in "hot spots" which are gene areas inclined to mutation. While certain hot spot mutations are common, some tend to be rarer.

Although tests implemented for detection and genomic profiling of such mutations which have great significance in treating cancer patients vary from simple to more complex tests, the importance of pathologic assessment here cannot be denied. The utilized technologies vary from immunohistochemistry, which includes pathologic assessments, to allele-specific PCR (polymerase chain reaction), Sanger sequencing, pyrosequencing, MLPA (multiplex ligation-dependent probe amplification) and next-generation sequencing, which are molecular genetic methods. Alterations in the number of gene copies can be detected with FISH (fluorescence in situ hybridization) or molecular karyotyping in addition to NGS.

In current practice, molecular profiling of the tumor starts with the isolation of circulating tumor DNA/RNA or the circulating cell-free tumor DNA/RNA from the paraffin-embedded tissue or peripheral blood (liquid biopsy).

Despite being rarer now, pan-cancer targets have also gained importance in clinical practice due to contributing greatly in patient treatment in addition to hot spot mutations. On the other hand, this condition, also referred as the tumor-agnostic approach, necessitates utilization of different diagnostic methods and algorithms. Considering the rareness of the genetic alterations to be detected, the method for the diagnostic process should be planned adequately in terms of patient's treatment and addressed elaborately with regard to patient benefit as well as the impact on established healthcare systems. Thus, it may be appropriate to first briefly discuss the advantages and disadvantages of the methods related to the tumor-agnostic approach.

Real-time PCR (RT-PCR) using the primer/probe pair which is specific to the investigated genetic alteration is among the most frequently used methods to detect the somatic mutation in tissue or liquid biopsy samples of cases with cancer. It is also a rapidly finalized and economic method that does not require any equipment other than those available in the majority of genetic laboratories. In this context, RT-PCR is a method with high sensitivity to detect predefined genetic alterations, providing great advantages in terms of costs and rapid results. However, it should be considered that RT-PCR does not detect the alterations in the tumor other than the targeted and known genetic variants.

As for the DNA sequencing method, although the Sanger method has been used intensively for many years and has undertaken the main role in the completion of the human genome project, its sensitivity is considerably low compared to RT-PCR, requiring at least 15-25 percent of the allele fraction needed to detect the mutation.

Another method used for DNA sequencing is pyrosequencing, which allows the sequencing of short-target gene regions and is limited due to the shortness of the sequenced region, providing a sensitivity of approximately 5 percent.

Among the conventional methods, the best known remains fluorescence in situ hybridization (FISH), which is still the most frequently used method to determine the number of gene copies and structural chromosomal alterations. This method uses fluorescence microscope for analysis and examines the target chromosome region or gene sequence. However, since chromosomal alterations are more common in hematologic cancers compared to solid tumors, it is generally used in the field of hematology. In solid tumors, this method is typically used for the detection of fusions.

Today, NGS technologies are gradually replacing all these conventional methods due to being more sensitive and safer compared to conventional genetic diagnostic tests. This method allows working on a greater number of genes simultaneously and reaching further information regarding the patient and the disease. This makes it possible to diagnose diseases with etiologies that involve multiple genes and screen a vast number of genes simultaneously in order to enable implementation of precision treatment options in fields such as cancer, thereby contributing significantly to patient treatment once the appropriate variants are detected in the patient.

Another significant contribution of NGS is transcriptome analysis (RNA sequencing), also referred to as transcriptomics, expressing the entire RNA sequence in a cell or tissue, thereby enabling highly sensitive detection of many alterations ranging from fusions to translocations using these systems. However, it should be noted that this method necessitates much more comprehensive analyses due to high data extraction. A safe and complete study would ensure correct reporting after the bioinformatic analysis and provide the utmost-quality healthcare services as part of the good medical practices.

On the other hand, in tumor-agnostic approaches, the disease diagnosis and patient needs are the sole determinants of the approach, biomarkers and technology to be used within the scope of good clinical practices.
Selecting a tumor-agnostic diagnostic method for routine implementation in the treatment of oncology patients is in fact a multi-step process for which adoption of the below steps is recommended to select the correct approach:

1) The Clinical Oncology Step: Assessment of all applicable diagnostic methods in accordance with the diagnosis and prognosis.
2) Laboratory Test Selection: By determining the benefits and testing limitations of the diagnostic method to be used, selecting the most beneficial method for the detection of genetic alterations that are significant for the patient in terms their treatment.
3) Clinical Reporting: Creating reports in accordance with the clinical status of the patient, including the sufficient level of clinical interpretation to be assessed at the oncology clinic.
4) Molecular Tumor Council: Performing advanced-level planning for certain cases, although not necessary in all patients.

In line with this algorithm, the key point in clinical approach is to primarily determine which test is requested for which purpose and have the awareness thereof. Molecular tests can be used in a wide range of fields including diagnosis, prognosis, target determination for treatment, and monitoring of treatment-related resistance mechanisms. Consequently, instead of the classic tumor councils, today's widely needed "Molecular Tumor Councils", including an oncology specialist, a specialist from the relevant surgical branch, a medical genetics specialist, a medical pathology specialist and a member from the bioinformatics team, should take part in the oncology clinic routine to determine needs, interpret test results and provide treatment.

Currently, a vast variety of methods are used in cancer treatment separately or in combination. Although the most common treatments of choice include surgical resection of the tumor (partial/total), chemotherapy and radiotherapy, newly identified biomarkers in cancer treatment and novel drugs targeting these biomarkers have brought forth the concepts of tumor-agnostic or pan-cancer, the major ones of which are presented in Table 2. Still, the search for biomarkers continue increasingly for several patients and diseases. In this respect, NTRK inhibitors constitute a good example. NTRK inhibitors are an efficient treatment alternative for many cancer patients in cases of detected NTRK1, 2 and 3 gene fusions. However, since NTRK1, 2 and 3 gene fusions are rare but may be seen in almost any common cancer, detection of these fusions would have a wide area of use in routine clinical practice, causing problems such as additional technical and economic burden.

NTRK gene fusions result from intrachromosomal or interchromosomal rearrangements between the 3' end of the related NTRK gene and the 5' end of the other relevant fusion partner gene. Here, what is important in terms of sensitivity to NTRK inhibitors is NTRK gene fusions, not NTRK gene point mutations. Also, these rearrangements may occur as loss of function, gain of function or inactive rearrangement. However, it should be kept in mind that gain of function is important in terms of NTRK inhibitors.

In recent years, although NGS in particular has been recognized as the gold standard as a molecular diagnostic method in oncology, detection of a pan-cancer biomarker using this method may constitute a great burden on healthcare systems while the shortage in qualified workforce in this field also confronts us as a risk factor in the attempts to allow the right patient access to treatment with the right outcomes.

To readdress the issue in terms of NTRK inhibitors specifically, we note that the incidence of NTRK1, 2 and 3 rearrangements should be primarily examined in adult and pediatric groups.

Table 1. NTRK1, 2 and 3 rearrangement incidences in Adult and Pediatric Tumors

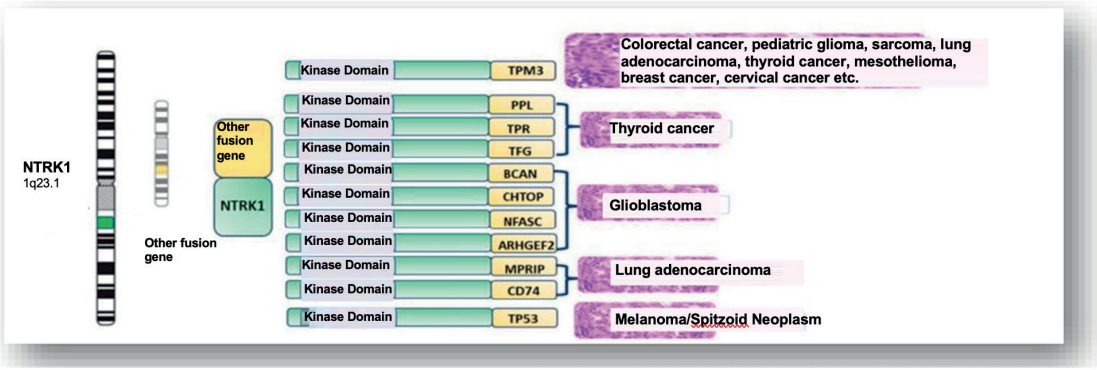
	Adult Tumors	**Pediatric Tumors**
<5%	Lung, Colorectal, Pancreas, Appendix, Cholangiocarcinoma, Melanoma, Glioma and certain Sarcomas	Glioma and certain Sarcomas
5-75%	Thyroid and Gastrointestinal Stromal Tumors (GIST)	Thyroid, Spitzoid Tumors and Congenital Mesoblastic Nephroma
>75%	Secretory Breast Carcinoma and Secretory Salivary Gland Tumor	Infantile Fibrosarcoma and Secretory Breast Carcinoma

Since NTRK gene fusions are detected at varied rates according to the age group of patients and the diagnosis, there is a need to plan diagnostic algorithms accordingly considering the principles of precision medicine.

Fusion partner genes, which are known and frequently seen in the literature for each NTRK gene as well as their corresponding clinical diagnoses should be assessed together and a road map should be driven considering patient benefit that will reach the diagnosis with the highest probability, thereby ensuring a beneficial model for the entire healthcare system.

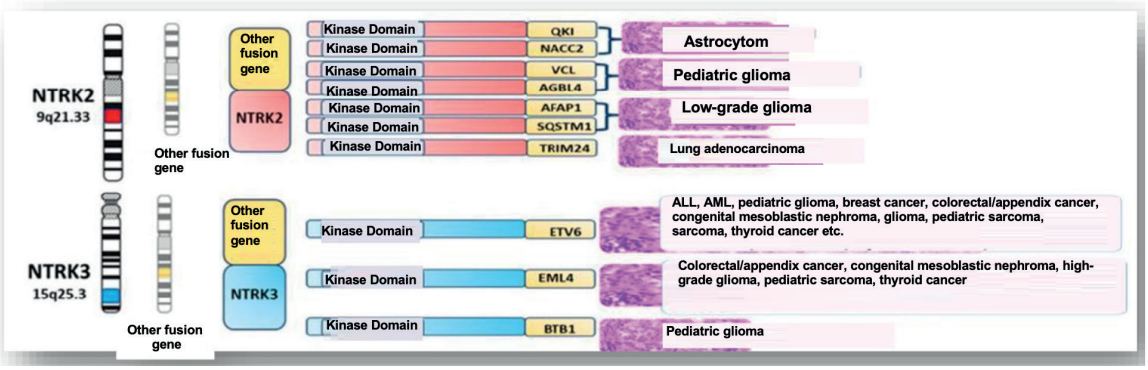
Clinical diagnoses in which NTRK1 gene fusions are frequently seen and the most common fusion partner genes of NTRK1 have been summarized below (Figure 5). While developing a diagnostic algorithm here, patient selection should be since NTRK1 fusions are detected at high rates in patients with detected ROS1, ALK1, RET, BRAF gene fusions.

Figure 5. Clinical diagnoses in which NTRK1 gene fusions are frequently seen and the most common fusion partner genes of NTRK1



Clinical diagnoses in which NTRK2 and NTRK3 gene fusions are frequently seen and the most common fusion partner genes of NTRK2 and NTRK3 have been summarized below (Figure 6).

Figure 6. Clinical diagnoses in which NTRK2 and NTRK3 gene fusions are frequently seen and the most common fusion partner genes of NTRK2 and NTRK3



In light of all of these information, two alternative paths emerge in front of us for each patient. While immunohistochemistry, FISH and real-time PCR may be implemented when the conventional path is chosen, NGS technology-mediated DNA-RNA sequencing may be implemented as part of the current approaches. However, awareness of the advantages and limitations of each path and method is the key element while determining the diagnostic approach. Below, these advantages and limitations have been listed under main titles.

1) IHC: It is a cheap, safe, rapid and common method that requires correct antibody selection. Also, due to its low sensitivity for NTRK3 gene fusions, recent recommendations by ESMO emphasize the need for molecular diagnosis in all cases with weak cytoplasmic staining.

2) FISH: It is the standard method particularly for the ETV6-NTRK3 fusion and should be implemented in primary care for certain diseases. However, due to its limitation in the detection of intrachromosomal fusions, patient selection should be made accordingly since the majority of NTRK1 gene fusions are intrachromosomal.

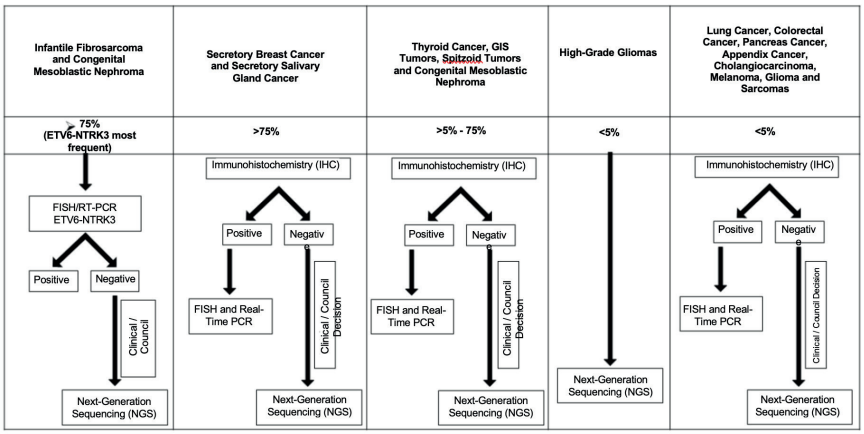
3) Real-Time PCR: It is a cheap and rapid method to detect known fusions, coming to the forefront with higher sensitivity compared to IHC. However, it should be considered that the condition should be assessed in terms of pathologic evaluations and other biomarkers, particularly in patients with limited tissue extraction.

4) Next-Generation Sequencing (NGS): Fusions can be detected with DNA- or RNA-based methods. However, DNA-based studies are technically limited to detect particularly NTRK2 and NTRK3 gene fusions. On the other hand, RNA-based studies should be carried out using a clinically validated and/or accredited method in a laboratory complying with good laboratory practices due to the challenges resulting from the pre-analytic processes in RNA extraction. Also, another issue which may be considered both as an advantage and a limitation is the assessment of whether the relevant test panel was designed only for the known fusions or for all fusions including the known or unknown and the feasibility of clinical reporting. One final important issue is the fact that NGS technologies have considerably variable sensitivity rates due to their 4 separate generations and different platforms. In this regard, the oncologist and patient should be informed of the standards at the serving laboratory.

One of the standard tests used to determine the tumor type and disease stage in cancer is tissue biopsy which demonstrates the cellular biological profile of the tumor at the time of diagnosis. For example, the cancer may be classified as small-cell- or non-small-cell-induced, which is a type of lung cancer, or as squamous cell or adenocarcinoma. This is the histology of the tumor and diagnosis can be established by using specific markers to help the treatment of choice for the tumor.

In current years during which a shift is taking place from personalized medicine to precision medicine, the need to adopt a disease-based approach has emerged, particularly considering the impact of tumor-agnostic approaches on patient survival. Specifically, while acting within the framework of "do no harm" principle to prevent abuse in the implementation of current technologies, sustainability of current healthcare systems should be prioritized as well. Therefore, patient's overall clinical information obtained because of all the analyses is valuable and may impact the result to be reported. Thus, below may be found the recommended diagnostic algorithm for the pan-cancer diagnostic processes specific to NTRK inhibitors.

Figure 7. Pan-cancer diagnostic algorithm



In oncology practice, the clinical benefit of "Genomic Profiling" has become unquestionable in terms of implementing personalized treatments, predicting possible adverse effects, assessing treatment efficiency, and reviewing possible treatment alternatives by detecting the resistance mechanisms during treatment follow-up. However, we need to address the issues that may confront us during routine implementation of all these processes and particularly in a tumor-agnostic approach. These issues and their possible solution recommendations have been listed below:

1) Numbers of Patients: Embedding algorithms particularly into diagnostic processes for the clinical follow-up of a high number of patients due to the tumor-agnostic approach, determining patient selection criteria and establishing multidisciplinary councils for decision-making in required cases,

2) Free Circulation of Biological Samples: Developing biological sample transfer systems and operating them together with an appropriate recording system in order to enable the right patient to access the right laboratory where the right methods may be utilized, thereby avoiding unnecessary retesting and keeping the tangible burden on the healthcare system under control,

3) Issues in Laboratory Implementations: Implementing practices/sanctions for the selection of methods and technologies to be used starting from the pre-analytic process and establishing laboratory quality standards,

4) Diagnosis and Treatment Decision Mechanism: Considering the current data, transformation of tumor councils to Molecular Tumor Councils, and ensuring continuity and currency via online systems in case of any shortage of specialists in the required area,

5) Clinical Interpretation and Practice: Preparing local guidelines for molecular data assessment for which sufficient time may not be allocated due to the intensity of patients and clinical workload,

6) Drug/Clinical Study Accessibility: Increasing joint collaborations to address regulatory and reimbursement issues and enhancing impact at the policy- and decision-maker level along with multidisciplinary and interinstitutional consortiums.

In conclusion, molecular biomarkers have become a standard and critical part of diagnostic approach to determine the optimal treatment in many solid tumors and avoid the potential toxicities of ineffective treatments. Table 2 below shows the evidence-based and clinically significant biomarkers and testing methods in frequently seen solid tumors.

Table 2. Evidence-based and clinically significant biomarkers and testing methods in frequently seen solid tumors

Non-small-cell cancer [19,20]				
Biomarker	**Specific alteration**	**Indication**	**Result interpretation**	**Testing method**
EGFR	Exons 18-21	For EGFR-targeting tyrosine kinase inhibitor (TKI) treatment	EGFR-targeting TKI response	PCR-based methods, NGS
	Exon 20 insertion	For EGFR TKI treatment	Primary EGFR-targeting TKI resistance Amivantamab	
	T790M	For EGFR tyrosine kinase inhibitor treatment	3rd generation EGFR-targeting TKI treatment	
ALK	ALK rearrangement	Assessment of treatment with targeted inhibitors	Response to ALK TKI inhibitor treatment	FISH, IHC, NGS, RT-PCR
ROS1	ROS1 rearrangement	Assessment of treatment with targeted inhibitors	Response to ceritinib and crizotinib	FISH, NGS, RT-PCR, FISH, IHC (screening together with FISH or molecular confirmation of positive IHC results)
BRAF	BRAF V600E	Assessment of treatment with targeted inhibitors	BRAF/MEK inhibitors (dabrafenib-trametinib) predict response Vemurafenib treatment in certain conditions	PCR-based methods, NGS
KRAS mutation	KRAS G12C	Clinical study for precision treatment	Response to KRAS G12C inhibitor treatment (sotorasib)	PCR-based methods, NGS
	Other KRAS mutation		Reduced probability to another actionable oncogenic alteration	
HER2 mutation	HER2 mutation	For treatments under development	Response to ado-trastuzumab emtansine and trastuzumab deruxtecan	NGS
MET	Exon 14 skipping alterations	For treatment with targeted inhibitors	Response to capmatinib, tepotinib and crizotinib	NGS, FISH (for amplification)
	High MET amplification			

RET	RET earrangement	For treatment with targeted inhibitors	Response to selpercatinib, pralsetinib (also cabozantinib, vandetanib)	FISH, RT-PCR, NGS
NTRK 1/2/3	NTRK rearrangements	For treatment with targeted inhibitors	Response to larotrectinib and entrectinib	FISH, İHK, RT - PCR, NGS

Colorectal cancer [21,22]				
Biomarker	**Specific alteration**	**Indication**	**Result interpretation**	**Testing method**
KRAS	KRAS mutation	For anti-EGFR treatment	Contraindication to treatment with panitumumab and cetuximab	PCR-based methods, NGS
NRAS	NRAS mutation	For anti-EGFR treatment	Contraindication to treatment with panitumumab and cetuximab	PCR-based methods, NGS
BRAF	BRAF V600; V600E, V600K	Prognostic	Worse prognosis compared to BRAFwt patients	PCR-based methods, NGS
		For anti-EGFR treatment	No response to treatment with panitumumab and cetuximab unless given with BRAF inhibitor	
		MMR-deficient tumors with MLH1 loss	Presence of mutation strongly supports a sporadic tumor; presence of BRAF mutations does not exclude the risk of Lynch syndrome. .	
HER2	HER2 amplification			
NTRK	Fusion	Treatment selection	Response to larotrectinib and entrectinib	NGS, FISH, IHC, PCR-based methods

MSI/MMR	MLH1, PMS2, MSH2, MSH6 loss of expression and/or MSI-high condition	Lynch syndrome screening	Considering genetic consultancy and germline testing (in the absence of BRAF mutation or MLH1 promoter methylation)	IHC, PCR-based methods
	MSI - high	Treatment selection	Better prognosis and ineffective 5-FU adjuvant treatment. Immune checkpoint inhibitor treatment	
MLH promoter methylation	MLH1 promoter methylation	MLH1 loss with IHC	Presence of MLH1 promoter methylation on a background of MLH1 loss shows sporadic origin.	Methylation methods
Gastric, esophageal and gastroesophageal junction cancers [23]				
Biomarker	**Specific alteration**	**Indication**	**Result interpretation**	**Testing method**
HER2	HER2 amplification	Trastuzumab treatment	Trastuzumab treatment	FISH, IHC
PD-L1	Expression	Immunotherapy	Immunotherapy	IHC
Pancreatic cancer [24]				
Biomarker	**Specific alteration**	**Indication**	**Result interpretation**	**Testing method**
BRCA1 and BRCA2	Mutation (somatic and germline)	Treatment selection	PARP and other DDR enzyme inhibitor	NGS
Prostate cancer [25, 26, 27]				
Biomarker	**Specific alteration**	**Indication**	**Result Tinterpretation**	**Testing method**

BRCA1 and BRCA2	Mutation (somatic and germline)	Treatment selection	PARP and other DDR enzyme inhibitor	NGS
ATM	Germline mutation	Treatment selection	PARP and other DDR enzyme inhibitor	NGS
Ovarian cancer [25,26,27]				
Biomarker	**Specific alteration**	**Indication**	**Result interpretation**	**Testing method**
BRCA1 and BRCA2, ATM, BRIP1 CHEK2 PALB2 RAD51C, RAD51D	Mutation	Involves other homologous recombination pathway genes and MSI or DNA MMR	Assists in guiding the treatment (e.g. PARP or other DDR enzyme inhibitors, chemotherapy response)	NGS
Breast cancer [25]				
Biomarker	**Specific alteration**	**Indication**	**Result interpretation**	**Testing method**
HER2	Gene amplification	Treatment selection	Response to HER2-targeting treatment (trastuzumab,	FISH-ISH
BRCA1 and BRCA2	Germline mutation	Treatment selection	PARP inhibitor treatment	
Central nervous system tumors [25,26,27]				
Biomarker	**Biomarker**	**Indication**	**Result interpretation**	**Testing method**

IDH1 and IDH2	Mutation	Diagnosis Prognosis Preadjuvant treatment	Good prognosis is associated with survival benefit when IDH1 or IDH2 is treated with radiation or alkylating chemotherapy and commonly associated with MGMT promoter methylation.	NGS
1p/19q codeletion	Deletion	Diagnosis Prognosis Preadjuvant treatment	Good prognosis Predicts response with alkylating chemotherapy alone and in combination with radiation	FISH
MGMT	Promoter methylation	Prognosis Preadjuvant treatment	Provides survival advantage even in IDH wild-type tumors in glioblastoma. Used in treatment decisions for elderly patients with high-grade (grade III-IV) glioma. Any patient with MGMT promoter-methylated glioblastoma obtains more benefit with temozolomide treatment compared to patients without MGMT promoter.	Methylation-specific PCR
Melanoma [25,26,27]				
Biomarker	**Specific alteration**	**Indication**	**Result interpretation**	**Testing method**
BRAF	Gene mutation V600E	Treatment selection	BRAF inhibitors	PCR-based methods and NGS
KIT	Mutation	Treatment selection	KIT inhibitors	NGS
Thyroid cancer [25, 27, 28]				

BRAF	Mutation	Treatment selection	BRAF-targeting treatment	
RET	Mutation	Treatment selection	RET inhibitor treatment	NGS, PCR-based methods
	Fusion			
NTRK 1/2/3 rearrangements	Fusion	Treatment selection	NTRK inhibitor treatment	RT-PCR, NGS, FISH
Gastrointestinal stromal tumor [25,26,27]				
KIT	Mutation	Treatment selection	Imatinib	NGS, PCR-based methods
PDGFRA	Mutation	Treatment selection	Avapritinib	NGS, PCR-based methods

Abbreviations: NGS: next-generation sequencing, IHC: immunohistochemistry, FISH: fluorescent in situ hybridization, TKI: tyrosine kinase inhibitor, RT-PCR: reverse transcription-polymerase chain reactionreaksiyonu

7. The status of Personalized Precision Medicine in the Healthcare Ecosystem

The value of novel drugs for patients and the society determines the pricing of innovative treatments and includes their broader benefit at individual, societal, and economic levels. Usually, the value of a drug is compared to both established and innovative treatments in their therapeutic areas. Factors that are taken into account include efficacy, life expectancy, quality of life, and reduction in other healthcare costs (such as inpatient treatments, length of stay at emergency department, office visits, diagnostic procedures, or even other [concomitant] medications).

Innovative oncology treatments can make a substantial difference for patients with regard to prolonging survival (reduced mortality), reducing the burden of disease (reduced morbidity), and maintaining and improving the quality of life.[17] Such drugs empower people affected by cancer to resume a comfortable family life and satisfying work life, carry out their daily activities, and be an active part of society, thereby decreasing the socioeconomic cost.

Whether tumor agnostic precision medicine will play a significant role in reducing the burden of cancer around the world depends heavily on how rapidly healthcare systems grant timely and affordable access to these drugs, diagnostic tools and the required infrastructure. When these elements are in place, tumor agnostic precision medicine confers long-term cost savings by replacing trial-and-error-based treatments, providing survival benefits compared to traditional standard-of-care treatments and allowing patients to avoid treatments that have limited efficacy and are poorly tolerated.

However, patients still face barriers of access, delays, and inequality across the remaining regions of the world. These barriers revolve around Health Technology Assessment (HTA) legislation, pricing issues, rare disease status and genome testing. HTA bodies have fragmented, non-standardized value-assessment methods that restrict patient access to newly approved cancer drugs. [29] There are a variety of factors that impede the use of effective drugs among clinically eligible patients and result in substantial loss of life years.

A review of examples from different countries reveals that in Japan, for instance, a novel drug receives a "usefulness premium" after a non-transparent assessment by the Central Social Insurance Medical Council (Chuikyo). As per the relevant legislation, the Response Rate (RR) and Adverse Events (AE) profile must be taken into account when determining the "usefulness premium". In practice, however, a limited number of drugs are all evaluated based on their Overall Survival (OS) results alone.[30]

China has a HTA system under development. Personalized medical products can be listed in the National Medical Insurance Drug Catalog via price negotiation organized by the National Health Security Administration (NHSA). The NHSA has released the work plan for the adjustment of the 2019 Edition of the National Medical Insurance Drug Catalog including procedures and key considerations. The work plan does not specify selection criteria and pharmacoeconomic assessment methodologies. It highlights affordability of the national medical insurance fund as a key consideration.[31]

There are ongoing studies in Europe regarding the barriers that prevent the full potential of personalized medicine products from reaching cancer patients.[32] For the European Union, despite the European Commission's recognition of the potential of personalized medicine in transforming cancer care, there appears to be significant disparities in patient access across Member States. According to the European Cancer Patient Coalition Report, personalized precision medicine approaches constitute the future of cancer treatments and should therefore be acknowledged as standard treatments. However, there are challenges across countries in access to biomarker tests, which cause delayed access to the required treatments. [33]

Currently, only certain patients in Europe have access to the 31 oncology drugs approved between 2006 and 2018. As a result of the low availability, clinicians are not able to fully utilize new cancer drugs and genomic testing methods. A recent study demonstrated that reimbursement decisions restricting access to licensed cancer treatments affected about 200,000 patients in 11 EU countries over a 10-year period.[34]

Recent progress in personalized precision medicine can be attributed to technological advances in genomic sequencing test panels, enabling more routine genomic studies of tumors in clinical practice.[35] A survey by the European Cancer Patient Coalition (ECPC) found that only one in four (23 percent) doctors feel that their patients are always fully informed about biomarker testing.[36] In many countries, there is a need to integrate tests into clinical practice. [37]

Denmark supports personalized medicine and precision treatments according to a "National Strategy for Personalized Treatment 2017–2020" and a developed personalized medicine infrastructure.[38] Like the United States, Denmark has prioritized personalized medicine, invested in testing infrastructure, and ensured that patients have access to both drugs and diagnostics (Dx). The U.S. Food and Drug Administration (FDA) approved NGS testing in November 2017. In March 2018, Medicare and Medicaid Services announced a decision to reimburse NGS for Medicare-eligible patients with advanced cancer.[39]

By including personalized precision approaches in patient treatment processes, pan-tumor treatments ensure that patients gain the utmost clinical benefit. The parameters to be evaluated while examining the clinical benefit presented by tumor-agnostic treatments may be listed as follows:

- Treatment efficacy and safety: It is recommended that the efficacy the treatment offers should be assessed in line with overall survival and progression-free survival data. In addition to the clinical benefit provided by the treatment, a low adverse effect profile is also a required value in the disease management process.
- Quality of life: A disease management process involving an efficient treatment plays a key role in the improvements achieved in patients' quality of life. Taking factors such as maintaining usual daily routines or participation at work into account, preserving improved quality of life aims to ensure that individuals are able to maintain their survival gains together with an improved quality of life.
- Cost analysis: When assessing pan-tumor approaches, long-term clinical advantages and cost savings provided by the achieved clinical outcomes should be examined while considering the evaluation of the total disease burden.
- Ethical assessments: Biomarker tests are an important step in determining treatments. Timely implementation of testing procedures in the right patients accelerates the diagnosis process, while enabling patient access to efficient treatment and maximum clinical benefit.

Since 2017, 3 pan-tumor treatments have been approved by the FDA, the authorized agency in the United States of America, and the EMA, the authorized agency in Europe. These treatments target tumor cells that emerge due to certain genetic anomalies. The aim is to implement personalized precision treatments and the relevant biomarker tests by focusing on the genomic mutations.

Table 3. Approved pan-tumor treatments

APPROVED PAN-TUMOR TREATMENTS			
Agent	**Biomarker**	**FDA Approval as of November 2020**	**EMA Registration as of November 2020**
Pembrolizumab	MSI-H or dMMR High microsatellite instability/mismatch repair deficiency PD-1 Programmed cell death protein 1	23 May 2017 Primary care of patients with unresectable or metastatic MSI-H or dMMR CRC	
Larotrectinib	NTRK gene fusions Neurotrophic receptor tyrosine kinase	26 November 2018 In adults and pediatric patients with solid tumors presenting with NTRK gene fusion	19 September 2019 In adults and pediatric patients with solid tumors presenting with NTRK gene fusion
Entrectinib	NTRK gene fusions Neurotrophic receptor tyrosine kinase ROS1 Receptor tyrosine kinase 1	15 August 2019 Adult patients with metastatic NSCLC with ROS1-positive tumors	28 May 2020 CHMP recommendation for registration as monotherapy in adults and pediatric patients aged 12 years and above with solid tumors bearing NTRK gene fusion expression

Regulatory and HTA bodies, as well as payers around the world that review, approve, evaluate, and reimburse medicines, are working hard to find ways to make innovative therapies accessible for cancer patients. The regulatory agencies in the EU, Brazil, Taiwan, Canada, and the United States have shown signs of willingness to accept novel trial designs and efficiently evaluate personalized medicine or tumor-agnostic treatments to encourage and accelerate the development of novel drugs. There are positive signs in the UK where the British National Institute for Health and Care Excellence (NICE) have shown an openness to new approaches to clinical trial designs. For example, in assessing innovative treatments, there is growing interest in basket studies which recruit patients based on the genomics of their tumor. However, countries need to adapt their regulatory, HTA and reimbursement legislation or regulations if they wish to make personalized medicine and efficient innovative treatments available to patients in their country.

Tackling delays in the approval, evaluation and reimbursement of personalized precision treatments will ensure faster and more equitable access for patients. This process can be accelerated by supporting the collaboration between regulators and HTA bodies on regulatory and reimbursement pathways for personalized medicine and precision treatments.

Any decision on the value of a novel drug should be based on transparent, scientifically sound, and predictable frameworks. Decision-maker bodies shall consider the medical importance and value of personalized medicine and precision treatments. In the meantime, innovative methodologies shall be developed to adapt to available evidence from novel trial designs (e.g. basket trials) and consider the significance of smaller data sets in treatment decision. Interim/ early access programs may allow the early provision of vital drugs while approval, regulatory affairs and value assessments and pricing negotiations are being conducted.

Uncertainties that exist at the time of drug assessment can be overcome if the assessment body requires additional evidence and data or processes for data collection and review (real-world evidence concepts). For the lack of comparators, flexibility should exist based on the medical needs.

HTA legislations should allow assessments to take novel endpoints such as Response Rate (RR) into account and not rely exclusively on Overall Survival (OS) results.
For patients, doctors, and healthcare systems, it is important that high-quality and broad gene testing, such as NGS, becomes part of routine clinical practice. Thus, patients can benefit from potential treatments.

In addition, a coherent national strategy should be developed for tumor agnostic treatments, planning genomic or comprehensive profiling for as many patients as possible, and outlining whether a greater number of patients can be screened using a broad targeted gene panel rather small or whole genome assays.

Since it is more cost-effective to use a broad test panel to simultaneously test for multiple genetic mutations driving cancer in patients compared to testing for one gene or a limited number of genes at a time, the development of such tests is also important.

In addition to all of these practices, countries should continue investing and cooperating in next-generation testing infrastructure as well as developing dedicated funding pathways to ensure access to diagnostics, personalized medicine and precision treatments. With the healthcare policy recommendations to be realized within the scope of a sustainable healthcare system, timely access of pediatric and adult oncology patients to personalized tumor-agnostic treatments will enable patients to achieve maximum clinical benefit and significant improvements in quality of life.

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