Personalized Medicine in Serbia

Opportunities and Challenges

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САВЕЗ ЕКОНОМИСТА СРБИЈЕ

Contents

What Is Personalized Medicine?

Research shows that ailments, such as heart disease, diabetes, and cancer, are significantly influenced by numerous genetic variations present within a single genome [27]. Treatments and prevention approaches that help certain patients may be ineffective or create adverse reactions for others. In practice, the traditional approach using preexisting general therapies and medications are usually provided based on average effects on the population of patients and trial-and-error approach. Such an approach is not always effective for all patients, and healthcare systems may provide inefficient care that fails to affect a patient's reaction to different treatments.

The current COVID-19 pandemic creates enormous pressures on already strained healthcare systems. Countries, including Serbia, are in dire need of new ways that can contribute to more efficient spending using a tailored approach to a patient's treatment compared to the one-size-fits-all approach. These changes will fundamentally alter the current underpinnings of public healthcare.

Personalized medicine represents a new paradigm shift in healthcare.

Personalized medicine is an evolving field that transforms biomedical and clinical research and basically all healthcare disciplines.[1] It provides a personalized and targeted approach to preventing disease and screening, diagnosing, treating, and curing patients by considering genetic and environmental factors as well as their lifestyles [17, 37].

Diagnostic testing and biomarker information analysis together with gathering and analyzing a massive data pool containing information of patients may be considered the core of personalized medicine.

Personalized medical treatments are determined based on novel and cutting-edge diagnostic tests. These tests enable the determination of significant unique molecular characteristics that may guide every phase of care (prevention, diagnosis, treatment, prognosis, etc.). Companion diagnostic tests also provide essential information regarding the appropriateness, security, and efficacy of specific treatment. Consequently, only those patients with specific test results are subject to admission of specific treatments.

Personalized medicine utilizes the vast amount of data (genomic, clinical trials, electronic health records, disease history, and drug intake, etc.) about thousands of patients available for various types of pooling and analyses. In that way personalized medicine enables treatments based on how other patients in similar positions and conditions have reacted. Physicians and data scientists combine this data with an individual's medical characteristics, and utilizing sophisticated models enable development of targeted prevention and treatment plans.

Personalized medicine helps the detection of the onset of disease, pre-empts the progression of the disease, and increases the efficiency of the healthcare system by matching treatments to only those who will benefit.

The biopharmaceutical industry has made a substantial investment in the development of personalized treatments. The industry has also embraced diagnostics as a tool for identifying which patients will respond to certain drugs [27]. The development and offer of personalized drugs, treatments, and diagnostics are accelerating. For example, nearly 35% of USFDA drug approvals in 2017 were personalized medicines. In the US, it increased from only 13 in 2006 to 286 personalized medicines, that is, drugs that point to specific

1 Personalized medicine is a rather broad concept. Other terms like precision medicine relate to similar (somewhat narrower) concepts and often tend to be used interchangeably [11].

biomarker(s) in their labels to guide use, currently on the market [26, 27].

According to the WHO data, the public spending on the health sector in 2018 accounts for almost 15,4% of all public expenditure in the EU. It also contributes 8% to the total workforce and 10 % to the EU's GDP. *In 2018, health expenditures in Serbia amounted to 8.5% of GDP and 12.5% of all government expenditure.* Hence, in Serbia, public spending on healthcare as a % of public spending is around two percentage points below the EU average. It is not only a question on how to increase spending, but even more importantly is to assess how to make it more cost-efficient.

The pressures to improve national health systems were building up even before the COVID-19 pandemic took hold.

As in other European countries [19], pressures related to the healthcare services delivery and financing in Serbia are connected to an aging population, the burden from cancer and chronic diseases, the cost of new technologies, and overall increasing demand for healthcare [5, 7].

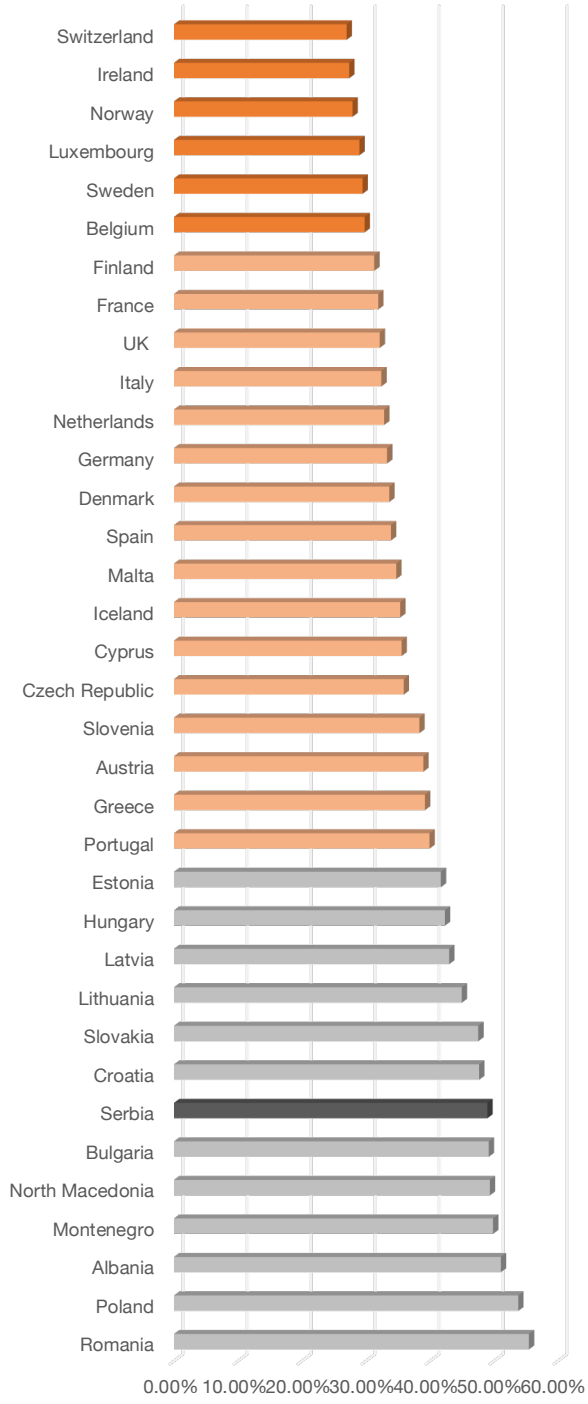
While health outcomes in Serbia have improved over time [13]*, some still lag behind*.[2] This includes mortality from cardiovascular disease and cancer mortality rates. While cancer mortality rates are declining, they still place Serbia among the countries with the highest cancer mortality in Europe [15, 16, 23], with almost 50,000 cases and 28,000 deaths annually.

2 In comparison of 35 European healthcare systems based on waiting times, results, and generosity Serbia is ranked 18th.

Cost-Effective Provision of Healthcare and the Advent of Personalized Medicine

Figure 1

Cancer mortality rates 2018



Source: IARC Cancer Today, 2018

The common goal in all countries is to define measures that promote cost-effective healthcare, including investment in e-health, e-care, and infrastructure [5]. However, besides these goals, both the EU and several member states have included specific mechanisms to ease access to personalized medicine [17].

The introduction of personalized medicine may require substantial changes compared to the conventional approach. It requires systematic transformation and substantial investments. Notwithstanding these costs and obstacles, many countries have started to adopt this novel technology. This adoption is not exclusive to advanced economies, as also several resource-constrained countries made the first steps toward the integration of personalized medicine. Most notably, ***the need to develop and increase access to personalized medicine is explicitly recognized as a goal by the European Commission*** [6, 32]. Since 2010 the European Commission has launched several initiatives to assess various aspects of personalized medicine, and regulations have been adapted to encourage uptake of and access to personalized medicine.

The integration of personalized medicine approach for all cancer patients in Europe is one of the goals of the Europe's Beating Cancer Plan adopted in 2020.

For example, ***Europe's Beating Cancer Plan*** and the ***Mission on Cancer*** of Horizon Europe have recommendations directly linked to personalized medicine (e.g., advancing, scaling, implementing, and optimizing personalized oncology and creating a European Cancer Patient Digital Centre where patients can deposit and share their data).

"The smart combination of health data and new technologies caters for the exponential development of personalized medicine, which becomes a powerful tool to address cancer through tailor-made prevention and treatment strategies, so patients receive the therapies that work best for them, and no money is wasted on trial-and-error treatments."

Europe's Beating Cancer Plan, European Commission (2021)

Several countries made substantial steps toward the integration of personalized medicine into healthcare system.

Denmark has invested substantial amounts in the research infrastructure of relevance to Personalized Medicine. Funds have been channeled to biobanks, genome sequencing equipment, and computers capable of processing large volumes of genetic information. Denmark introduced the *National Strategy for Personalized Medicine for the 2017-2020 period*. The strategy is based on several principles, including a focus on the patients, confidentiality, and economic sustainability of personalized medicine as a standard offer in the healthcare system [3].

The UK has attempted several initiatives to shift from population-centered to individual-centered approaches [28]. The UK was also a frontrunner with the adoption of *the Stratified Medicine Program.* The aim was to "*ensure standardized, high-quality, cost-effective genetic testing of tumors is available for people with cancer*" [21]. ***More recently, the UK adopted an ambitious program - Genome UK The Future of Healthcare***, where the first pillar - Diagnosis and Personalized Medicine aims to incorporate the latest genomics advances into routine healthcare to improve the diagnosis, stratification, and treatment of illness [14].

Other European countries also made significant steps to enable wider assess to personalized medicine. For example, France has facilitated timely access to personalized medicine to allow patients to receive early access to medicines that have not yet received marketing authorization [11]. However, personalized medicine integration into the health system and prioritization dif fer, and there is a substantial gap between frontrunners and other countries.

The German National Center for Tumor Diseases (DKFZ) is a well-known research center that strives to offer each patient a personalized treatment option specifically tailored for his or her individual needs. DKFZ collects and analyses patient data such as clinical information systems, tumor registries, biobank systems, and other records to enable personalized treatment for each patient.

DKFZ: https://www.dkfz.de/en/dkfz/quick-facts.html

Faced with the Covid-19 pandemic, and due to an increase in demand for healthcare due to the aging population and chronic diseases, the Serbian health system has to achieve resilience and sustainability to future shocks.

Serbia has made several efforts during the last years to increase patients' access to innovative therapies and narrow the gap with advanced countries.

In the foreseeable future Serbian health systems will require additional investment to address healthcare challenges and provide personalized medicine over the longer term. While it will take time to incorporate fully personalized medicine into the healthcare system, access to personalized medicine in Serbia is hampered by several regulatory barriers. Yet, Serbia has an excellent predisposition and human resources that are necessary for genomic- and biomarker-informed treatments.

In what follows, we will describe the potential benefits of personalized medicine finance, funding, and regulatory issues - how investment in the system could be encouraged and how some regulatory hurdles may be removed. Finally, we present a potential roadmap to enable and incentivize the adoption of personalized medicine in Serbia.

Potential Benefits of Personalized Medicine

There is a clear need to explain potential benefits and opportunities to consider personalized medicine issues, especially to policymakers. ***Personalized medicine could substantially improve health outcomes, reduce costs to the healthcare system and deliver additional economic benefits*** [10, 36]. Understanding the relative benefits and costs of personalized medicine is vital to ensure that patients receive effective and economically efficient services [9].

Of course, personalized medicine is not a panacea. The rationale for personalized medicine is rather sound but is hampered by shortcomings in the existing evidence base. Genomic- and biomarker-informed treatment and resulting health system efficiency are still under investigation. But the literature recognizes a number of opportunities and benefits linked to personalized medicine. The most helpful way to overview benefits is to classify them into several categories.

Benefits for patients

For patients, personalized medicine may lead to several specific benefits. First, personalized medicine should improve efficacy as the timely prescribed medicines can expect better outcomes and increase overall survival rates. Pharmaceutical interventions are often not effective in a substantial percentage of patients due to differences in the way an individual responds to and metabolizes medicines. By evading 'trial-and-error' and moving to timely prescription of optimal therapies personalized medicine delivers better response by the patient and increases the patient's well-being.

Second, personalized medicine delivers significant benefits by reducing the frequency and magnitude of adverse drug reactions. In a nutshell, personalized medicine may predict what medications at what doses will be effective and safest for individual patients based on their genetic profile. By looking at a genetic variation, personalized medicine enables safer and more effective drug dosing.

Third, personalized medicine increases patient's adherence to the treatment. Patients may have a higher likelihood of complying with their designated treatments in cases where personalized treatments are more effective or cause fewer side effects. As recently stated, the strongest effect could be in the treatment of chronic diseases, for which non-adherence commonly exacerbates the condition [27].

Fourth, in some cases, personalized medicine may reduce high-risk invasive testing procedures. Instead of more expensive, invasive and uncomfortable procedures (e.g., tissue biopsies), patients may benefit from personalized medicine solutions.

In addition, personalized medicine paves the way toward more *patient-centered care* [11]. However, such approach requires that patients be held more responsible in case they do not adhere to their treatment.

Benefits for healthcare system and socioeconomic benefits

The healthcare system is operating within an increasingly budget-scarce environment. Personalized medicine has the potential to improve outcomes for patients while helping to control the overall cost of healthcare. Personalized medicine may help decrease the overall costs associated with several inefficiencies - costs due to trial-and-error dosing, costs due to adverse drug reactions, costs due to late diagnoses, and costs due to reactive treatment [27]. The potential cost-effectiveness of personalized medicine strategies is dependent upon proper implementation. More specifically, literature usually lists several benefits to healthcare systems.

First, personalized medicine facilitates better prediction and management of a disease.

Personalized medicine has the potential to lower overall healthcare costs. This implies higher short-term costs (due to usage of companion diagnostics) but lower long-term costs. As recently emphasized, identifying which patients should and should not be treated with targeted treatment can save tens of thousands of dollars per person [11].

Second, personalized medicine may reduce the hospitalization rate. The use of personalized medicine may decrease the average hospital stays length to an average of 3-4 days for those using personal oncology therapies compared to an average of a week for those treated with chemotherapy [11].

Third, personalized medicine may prevent or delay more expensive care costs. Recent research showed that, between 2008 and 2017, €459.6 million was saved on treatment by investing approximately €11 million. By testing for EGFR biomarkers in over 16,000 lung cancer patients in France in order to determine who would respond to available treatments (gefitinib or erlotinib). Global annual waste because of misdiagnosis amounts to as high as $350 billion [11].

The increasing use of personalized oncology therapies led to a decreased number of stays and indirect savings. For example, analysis has shown that the mean incremental savings to society per patient receiving bevacizumab plus chemotherapy treatment for non-small cell lung cancer were €2,277 in Italy, €2,695 in Spain, €3,350 in France, and €4,461 in Germany. Personalized oncology was found to yield more savings compared to standard chemotherapy in terms of increased productivity and decreased social benefits paid to patients who were able to return to work in France, Germany, Italy, and Spain

Gill et al. (2020).

Beyond the healthcare system benefits, personalized medicine can have a substantial socioeconomic impact. Ensuring that health outcomes improve as the population ages can significantly reduce future spending pressures. Overall, if patients are offered targeted treatments, annual healthcare savings can be considerable. This may result in better prediction of patient responses to treatment, reduced potential for adverse events, and reduced costs [11].

Challenges Raised by Personalized Medicine

Despite significant potential benefits, personalized medicine is faced with a number of challenges [20]. Integration of personalized medicine into the healthcare system requires adequate funding and regulatory framework. Besides funding and regulatory issues, personalized medicine also raises several ethical questions. All these issues require a more detailed examination. Due to limited space, we will restrict our attention to funding, payment, and regulatory issues.

One should make a clear distinction between financing issues and payment models. Financing refers to the source of funding (state, payer, or patient) and how the funding is secured [4]. Payment models refer to how the therapy will be paid. Hence, besides funding-related issues, Serbia should assess innovative payment and reimbursement schemes.

FINANCING ISSUES REGARDING PERSONALIZED MEDICINE

How to cover the high targeted costs? How to assess and justify the value-added of personalized medicine compared to standard methods? The answer to these questions is complex and depends on the level of development of the economy and healthcare system. While some solutions applied in other countries represent useful direction, often they cannot be easily and fully transferred. Nevertheless, even though some therapies are well beyond the reach, Serbia should evaluate opportunities and challenges for the implementation of personalized medicine in practice.

Fiscally sustainable funding

The financing of personalized medicine through compulsory health insurance or the state budget could be justified with the need for enforcing solidarity. Otherwise, the use of out-of-pocket financing of personalized medicine would not enhance the public healthcare system but disintegrate it to a great extent [31].

Costs needed to cover personalized medicine from fiscal resources must not undermine fiscal sustainability [37]. On the one side, spending on personalized medicine may allow Serbia to improve health outcomes while not increasing overall costs or even create savings in the long term. On the other side, the cost could become expensive or even unaffordable and diverting taxpayers' money to little or no purpose.

A recent proposal that should be taken into consideration establishing a special fund aimed at financing innovative medicines [24]. Such fund could be established either by a decision of the Government or an amendment to the Law. Of course, a careful examination and lessons learned from other countries should be used in a case such fund is to be established. Any budget reallocation needs to be based on a thorough assessment of sustainability and should be aligned with macroeconomic conditions. Some of these assessments may be supported by international development agencies.

Reducing system waste in the Serbian healthcare system may release funds that can be used for personalized medicine solutions.

Public funding should also enable faster integration of personalized medicine into the healthcare system. The state could also provide fiscal incentives and/or funding for businesses

(e.g., biotech companies, diagnostic and IT companies) and academia that see personalized medicine as a part of their business model or research interest. WEF survey of funding possibilities [37] identified a broad array of potential modalities. For example, some kind of public support can be offered in the form of "push" funding (up-front reimbursement of research, development, and production expenditures, tax incentives) or "pull" funding (payment for successful outcome). Although both types of support come with a caveat, pull funding system, rather than a push system based on direct cost reimbursement, could better serve to accelerate the application of personalized medicine in Serbia. Some funding for specific activities may come from international development assistance (for example, in the EU in the 2014-2016 period, the European Commission invested app. €2.4 billion in innovation regarding personalized medicine).

Finally, besides public funding, a number of healthcare systems in EU members "are increasing provided by a combination of public and private healthcare providers and paid by a combination of public and private insurance, including co-payment by patients" [4].

Payment models

Closely related to funding issues are questions related to the payment models. In order to promote the rights of patients to access personalized medicine, it is necessary to understand how payment and reimbursement schemes may be developed and implemented [22]. Payment models may provide access to personalized medicine while managing financial and performance uncertainty. Payment and reimbursement policies vary across Europe.

A number of countries use so-called managed entry agreements (MEAs), also known as risk-sharing agreements, special pricing arrangements, or patient access schemes.

Some countries place more emphasis on clinical outcomes and clinical benefit whilst others are more focused on cost-effectiveness [11]. In Serbia, the legislation enabling MEAs was introduced in 2014, and the first MEAs were signed in 2016 [8].

Current Rulebook on Conditions, Criteria, Manner and Procedure for Placing the Drug on the List of Medicines, Modifications, and Supplements of the List of Medicines, or Removing the Drug from the list of Medicines (Official Journal n. 30/2010, 107/2012 and 113/2017) in its Article 9, paragraph 1 allows: 1) „risk-sharing" agreements; 2) „volume-cap" agreements; 3) „value-cap" agreements; 4) „cost-sharing" agreements; 5) other agreements that are allowed by the Law on Competition Protection.

- Conventional approaches

The more conventional approach would be to use financial agreements that are not linked to the performance of treatments and do not require the analysis of data related to health outcomes [35]. These agreements may be structured in various ways. First, a producer may charge the list price or provide a reduction off the price (up-front discount or an ex-post rebate refunded by the firm). Second, agreements may be based on the patient or population level expenditure. At the patient-level, agreements may set expenditure thresholds that would trigger discounts or provide products exceeding the cap free of charge. An inverse approach is also possible. Namely, the initial treatment may be free, but additional units would be purchased at an agreed price. In case that agreements are population-based, they may set expenditure caps for all or targeted patients, after which the supplier provides products exceeding the cap

free of charge. Alternatively, the agreement may introduce tiers (price-volume agreements) so that the increasing purchases will decrease prices. Finally, agreements may also set utilization caps that would set thresholds – a maximum period or dosage for the treatment to be efficient.

- Outcome-based models

Outcomes could be defined in terms of a positive health outcome or evading an adverse event [1]. Outcome-based payment models may take different shapes.

Outcomes-based payments conditioned on performance and are related to observable outcomes, providing incentives to deliver the most effective treatments.

These pay-for-performance schemes would provide payers with the opportunity to pay the manufacturer only in the case of success that would be defined by both parties. ***Essentially, such models are based on risk-sharing providing for higher reimbursements for better outcomes and lower reimbursements for reduced outcomes*** [25].

Outcome-based agreements may be specified at the patient or the population level. Payment to the supplier may be contingent on the achievement of a pre-determined response to treatment. Hence, until the agreed result is achieved payer may receive a refund or additional free treatments. Similarly, coverage of the treatment may be provided only for patients who achieve pre-specified response [25]. Often, the treatments are temporarily covered for patients who enroll in a study that evaluates the performance of the treatments.

Agreements specified at the population level may be covered temporarily by the payer for all treatment eligible patients, contingent on the achievement of an agreed result in the population treated [35]. In case the results are not achieved, the payer may withhold payment or may receive a refund or receive additional products free of charge.

Besides treatments, other options may be applied in the case of genomic testing. Namely, increasing routine genomic testing that should guide treatment or eligibility for clinical trials, may require complete coverage. In practice, that could mean that diagnostic test is reimbursed for all e.g., cancer patients and the treatment would be subject to assessment.

In Serbia, new examination and treatment methods may only be provided if the Commission formed by the Health Insurance Fund approves the use of innovative drugs based on a previously submitted proposal of the competent health institution to introduce the drug into therapy. The Commission includes the most recognized experts for diseases for which innovative therapy has been requested. The Commission examines their therapeutic impact, effectiveness, and medical necessity.

Generally, there is a trend towards the outcome- and value-based pricing and reimbursement models in many countries [18]. However, outcome-based agreements are resource-intensive, and more challenging to implement. They require the successful implementation of sophisticated IT solutions and electronic clinical records linked to reimbursement systems [8].

Experience with outcome-based models in EU member states suggests good practices that could be implemented in Serbia.

According to Wenzl and Chapman [35], such agreements should be used strategically and only where the benefit of additional evidence on product performance in terms of improved resource allocation outweighs the cost of negotiating and executing agreements. Designing performance-based agreements is not an easy task, and they should not be used when more appropriate means of providing coverage to personalized medicine are possible.

Bringing personalized medicine to the Serbian healthcare system may require procedural changes to the payment and reimbursement landscape and determine how best to pay for personalized medicine.

The first and tangible steps are already taken. So far the Serbian Health Insurance Fund (HIF) has incorporated eight personalized medicines on its Reimbursement List, all of them via different types of MEAs and posterior to the transparent process of negotiations with pharma companies.

Serbian authorities should gradually proceed with providing extended access to personalized drugs to insured persons of HIF. It might be wise to first implement tests in therapeutic areas within which there is already high availability of innovative drugs in place (e.g. lung cancer). On the other side, pharma companies should facilitate the process and give a hand to HIF by enabling greater concessions than usual for personalized drugs, notably for their off-label use. These concessions would be formalized through pertinent MEAs. This can serve as an illustration of how to build a partnership between the payer and the industry. The payer is to make off-label use of personalized drugs more flexible as described below (this is a condition sine qua non for integration of personalized medicine into health system), and pharma companies are to respond via significant adjustments of their price policies, specifically if off-label use of medicines is in question.

REGULATORY ISSUES REGARDING PERSONALIZED MEDICINE

One of the major impediments in integrating personalized medicine is the lack of sufficient legal options for its use. There are different barriers and challenges to the adoption and enhanced implementation and uptake of personalized medicine. For example, countries face issues related to access disparities due to various regulatory practices that affect pricing and reimbursement systems for both medicines and diagnostics, a lack of precedence for new treatment paradigms in the regulatory process and incompatible requirements, etc [11].

The regulatory framework for personalized medicine is still emerging. The lack of a clear framework may discourage investment in the field [27]. Still, some visible improvements (e.g., the regulatory framework affecting genomic- and biomarker-informed treatment have changed in recent years to keep pace with continuous changes in this field. Serbia is not different.

• Controlled off-label use of medicinal products as a primary challenge to the implementation of personalized medicine

Legislation on medicinal products regulates the market access of these products by setting standards of safety, quality, and efficiency. The terms under which a medicinal product can be used safely and efficiently are established during the marketing authorization procedure [34]. Personalized medicine may imply the off-label use of medicinal products. The term “off-label use” refers to any intentional use of an authorized product not covered by the terms of its marketing authorization. For example, this may be the use for a different indication, use by a different patient group, use of a different dosage, or use of a different method of administration. This is especially the case for rare diseases, rare medical situations, severe diseases, or other medical situations that are difficult to treat, therefore invariably in specific patient groups [34]. The off-label use thus increases the opportunities to treat specific patients. However, as a sensitive and delicate regulation field, off-label use must reconcile the best interest of individual patient treatment

outcome as well as his/her protection from potential experiments and medicines misuses.

• EU legislation and case-law

For Serbian legislators, market participants, and patients, it is important to understand the European Union legal framework for medicinal products, given the country's aspiration to join the Union. The duty of the Republic of Serbia to harmonize its national legislation with that of the European Union stems from the Stabilization and Association Agreement signed with the EU in April 2008. The EU law aims at partly harmonizing national legislation in the pharmaceutical sector, in particular with a view to safeguarding public health. The requirement of a marketing authorization is a general rule in the legal framework of medicinal products. According to Article 6(1) of Directive 2001/83/EC on the Community code relating to medicinal products for human use (Official Journal n. L311, 2001), it is in principle prohibited to market medicinal products without marketing authorization.

However, EU law does not regulate the way medicinal products are used in clinical practice. Therefore, the prescribing/administering of a medicinal product, on-label or off-label based, is a decision taken within the relationship between a patient and his or her treating healthcare professional/s. As stated in the Article 168 (7) of the Treaty on the Functioning of the European Union, the ultimate responsibility for the definition of health policy and the delivery of health services and medical care lies with the Member States. The General Court of the European Union also confirmed that off-label prescribing is not prohibited or even regulated by EU law, and that there is no provision that prevents doctors from prescribing a medicinal product for therapeutic indications other than those for which a marketing authorization has been granted (case T-452/14, *Laboratoires CTRS v Commission*, paragraph 79) [34]. There are, however, some EU pharmacovigilance requirements that extend to off-label uses. For example, the Member States and marketing authorization holders are required to obtain and provide data regarding suspected adverse reactions arising from the use of medicines outside the terms of the marketing authorization [12].

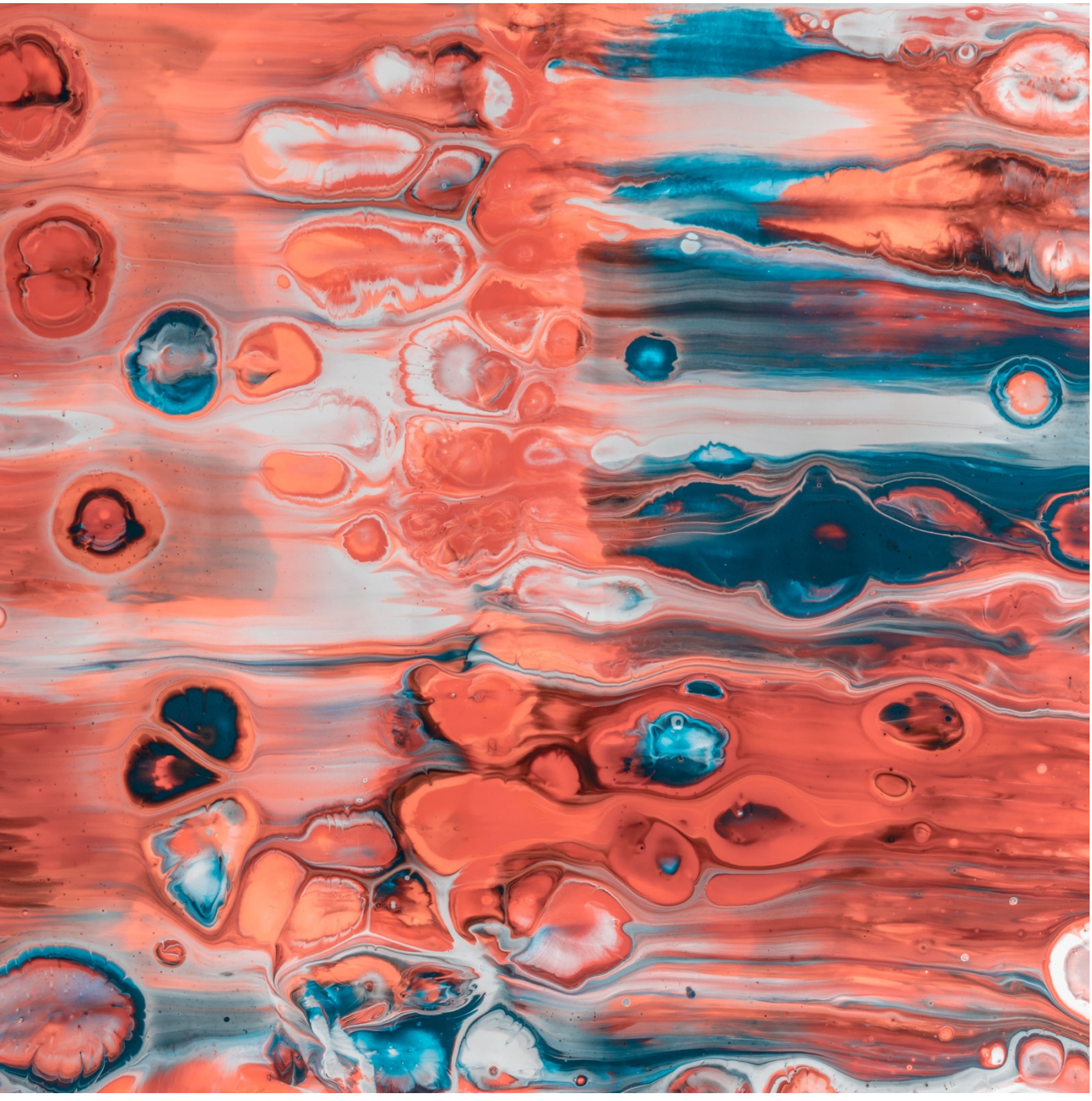
• Removing off-label use impediments as a prerequisite for the wider presence of personalized medicine in clinical practice

In a manner similar to EU law, the Law on Medicines and Medical Devices of the Republic of Serbia (Official Journal n. 30/2010, 107/2012 and 113/2017) in its Article 134, paragraph 1, prohibits the sale of a medicinal product if the latter has no medicinal product permit, and/or if it is not registered in the Medicines and Medical Devices Agency of Serbia registry in accordance with this Law. However, the Serbian legal framework already allows for exceptional off-label use of medicines, with the consent of the patient, at the initiative of the medical doctor and upon approval from the Ethical Board of the referent medical institution. Given the health but also economic benefits arising from the off-label use of medicines, as shown in this paper, one could consider the further improvement of the legal framework, for instance, by explicitly allowing for off-label use of medicines based on the results of certain highly sophisticated testing such as comprehensive genomic profiling.

Comprehensive genomic profiling (CGP) is a next-generation sequencing (NGS) approach that uses a single assay to assess relevant cancer biomarkers for therapy guidance. By using comprehensive genomic profiling, it is possible to map an individual's unique genomic profile. These insights provide invaluable information to physicians that can help them determine the best possible treatment for each patient which, in certain cases, may point to the

off-label use of a medicine. As this type of testing explicitly provides the result containing the name of medicine proven the most effective therapy option in a number of similar clinical cases deposited in corresponding databases, this should be considered evidence-based decision-making. As such, this kind of proceeding in clinical practice meets the criteria of safety and efficacy in patient treatment. Out of all mentioned reasons, legal grounds for off-label use based on results of different types of sophisticated testing must be constituted in the period to come. That way, one of the first and major steps towards personalized medicine implementation would be taken. Further development of personalized medicine would undoubtedly contribute to one of the objectives of the Strategy of Public Health in the Republic of Serbia 2018-2026 (Official Journal n. 61/2018), which consists in establishing an innovative, efficient, and sustainable national healthcare system.

Roadmap for the Integration of PM into Serbian Healthcare System



There is an increasing interest among researchers and physicians in personalized medicine in Serbia. However, the Serbian healthcare system is still facing certain issues in providing basic healthcare services. Consequently, the current personalized medicine adoption is haphazard/sporadic, and not initiated by the system. In this context, it might be said that some aspects of personalized medicine are present through medical research and some area of clinical practice, most notably in the field of oncology.

As elaborated in the second section, several countries and international associations launched initiatives with the aim to adopt and facilitate personalized medicine. These initiatives provide principles and guidance on key steps for the roadmap.

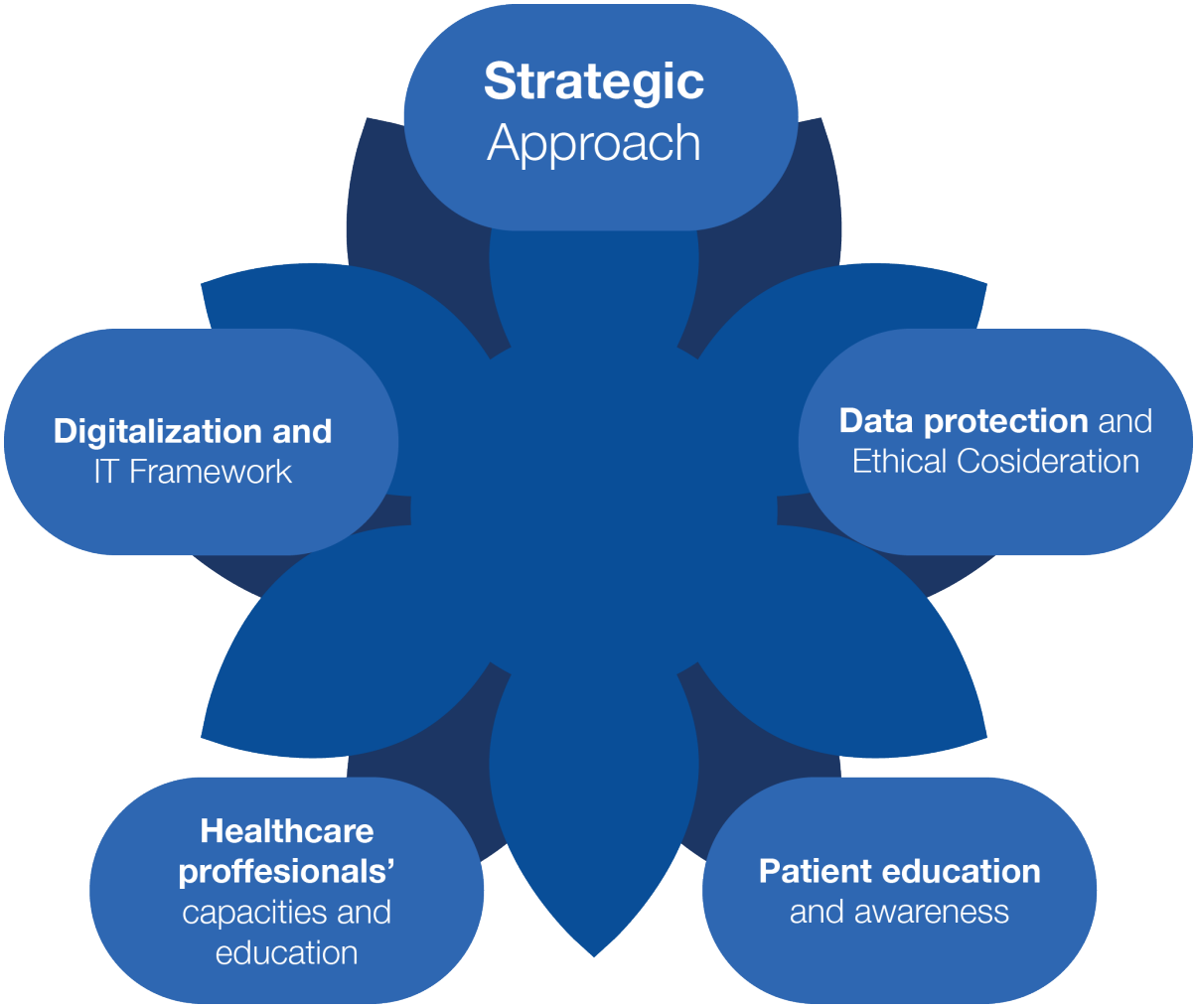
To adopt personalized medicine as part of the future national health agenda, ensuring sustainable funding and consistent political support are central for building expertise and infrastructure at both research and clinical settings [2].

The Consensus Paper on the Building Blocks for Personalized Healthcare [29] emphasizes four building blocks. Firstly, personalized healthcare requires a strong vision, implementation strategy that needs to be put in place, and collaboration to become a reality. This also includes raising medical staff knowledge patient awareness and providing incentives to participate, provide value-based care, and share data. Secondly, it requires conducive health information and an underlying IT infrastructure capable of providing the data, technologies, and standards to accelerate personalized healthcare. Such infrastructure coupled with clear legal and ethical rules on data sharing could accelerate access to personalized healthcare. Thirdly, new and innovative models in all health services and settings should be structured around the use of best-practice diagnostics and other personalized health infrastructure, with a patient-centric care model and integrated care coordination. Such an environment would leverage new technologies to improve patient health and outcomes. Last but not least, health products should be framed to enable personalized healthcare. This requires changes in the regulatory framework, including well-defined health technology assessment and pricing and reimbursement (P&R) mechanisms.

For example, the World Economic Forum Platform for Shaping the Future of Health and Healthcare launched the Precision Medicine Readiness Principles. The Readiness Principles are to serve as a roadmap that allows relevant stakeholders to evaluate their health system's capabilities with regards to implementation and further innovation in the area of personalized medicine [37]. Additionally, the abovementioned Consensus Paper on the Building Blocks for Personalized Healthcare [29] differentiates four building blocks of personalized healthcare into seventeen individual sub-blocks and fifty elements.

For a country with Serbia's level of economic development, it is desirable to define and standardize procedures and solutions that are achievable and acceptable for the integration of personalized medicine in its healthcare system and health culture. These building blocks and principles may also be validated in the Serbian context. They may provide a baseline that defines functions and roles of policy, business and healthcare leaders, and other relevant stakeholders and participants of the Serbian healthcare system with regards to enablement of a more personalized approach to the prevention, diagnosis and treatment of diseases.

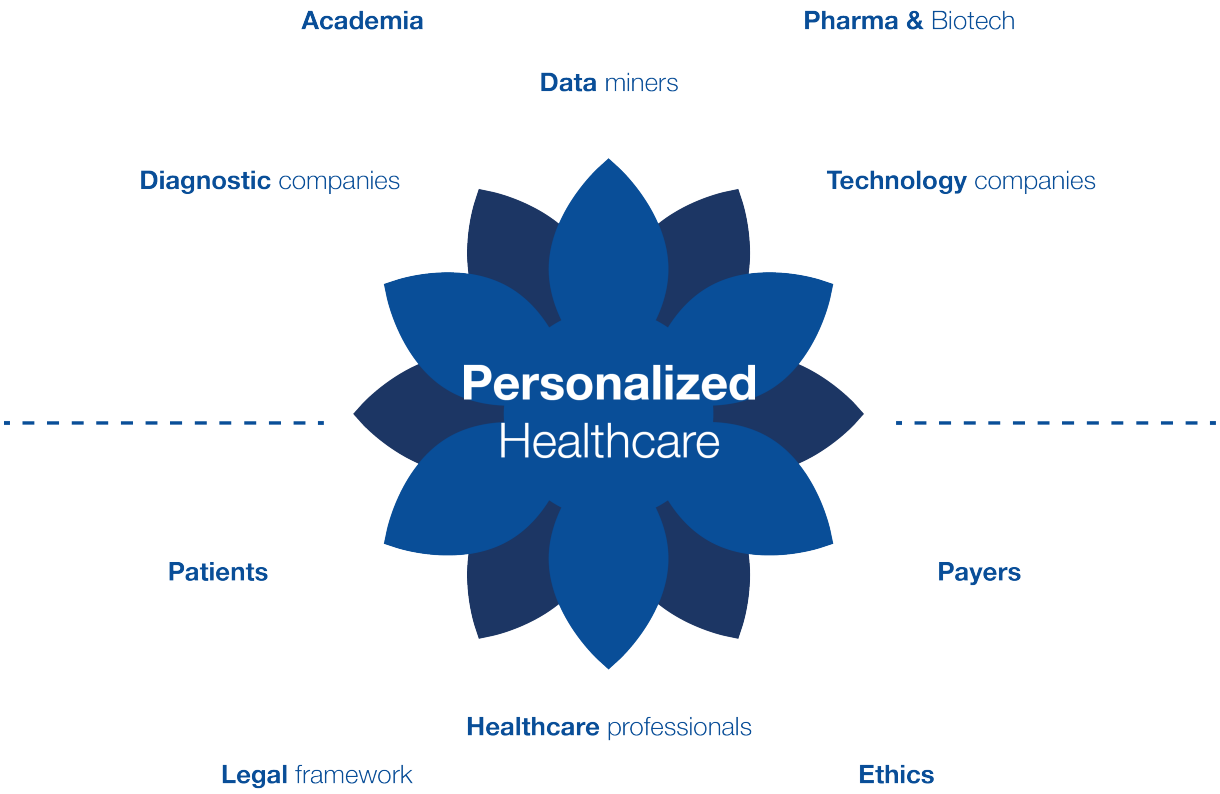
Figure 2 Building Blocks



- A strategic approach to Personalized Medicine

In order to support a comprehensive and long-term inclusion of personalized medicine practices into the Serbian healthcare system, an actionable and sustainable approach needs to be put in place. The role of the Government as a key stakeholder is highlighted when it comes to necessary regulatory shifts and national support in the implementation of personalized medicine as a standardized practice in healthcare. In that sense, the development of a national policy document (programme) for the implementation of personalized medicine practices in Serbia is desirable. Throughout the process, different stakeholders, including those from the pharma industry and international organizations, may provide invaluable experience and advice to decision-makers when it comes to a better understanding of opportunities of personalized medicine and economic and public health benefits that may arise.

Figure 3 Personalized Medicine Stakeholders Space



Adapted from Jakka, Rossbach (2013).

The precondition for this step is to have a common understanding of personalized medicine, its scope, and expected outcomes and communicate the benefits of personalized healthcare. Such Programme should assess sustainable funding methods discussed in the previous section and define necessary investments targeted towards areas with the highest cost-effectiveness. The strategy should be action-oriented yet flexible.

Key public policy measures incorporated in the strategic document should induce implementation, define procedures, create sufficient incentives; ensure transparency; achieve diagnostic and treatment efficacy and impact; provide patient access; ensure sustainability and flexibility.

Personalized healthcare provides immense opportunities for the collaboration of stakeholders in the personalized healthcare ecosystem. Stakeholders can co-create and innovate through collaboration using knowledge-sharing networks, technology transfers, incubators and accelerators, biotechnology clusters, public-private partnerships, genomics partnerships models [29, 37].

- Digitalization and IT Framework

Digitalization and rapid advances in data gathering and analysis provide an immense opportunity for more efficient retrieval and exchange of data in real-time, enabling more cost-effective treatments and personalized care pathways [18]. The functional electronic health

record system is an important tool in the adoption of personalized medicine. In Serbia, the digitalization of different aspects of the healthcare system and procedures is already underway, but substantial improvements need to be yet implemented [24].

More recently, Serbia made a major step towards creating a comprehensive and strategic approach to digitalization. Namely, drafting the *National Programme for eHealth development* is underway. This *Programme* should provide clear directions for amending the legal framework and introducing state-of-the-art technological solutions in the Serbian healthcare system.

Personalized medicine represents an opportunity for venture capital to invest in parts of the personalized medicine ecosystem. Currently available equity-based financing sources are very limited in Serbia [33]. Yet, the personalized medicine ecosystem, including necessary infrastructure, could be a candidate for those who are willing to bear the risk and reap potentially high rewards. Although private equity financing that provides funding to more mature companies would probably lack candidates in Serbia, some companies could be recipients of such funding.

The coordinating body in charge of the digitalization of the Serbian healthcare system will indeed aim to achieve significant cost savings. For example, it is estimated that in most European countries, the digitalization of medical services may cause a decrease in health expenditures by an app. 5% [30].

Proposed digitalization measures should be compatible and consider specificities of personalized medicine. Namely, there are numerous prerequisites for the collection and sharing of medical data that may facilitate the integration of personalized medicine in a secure and efficient manner:

- Appropriate IT infrastructure that allows the development of digital platforms, easier sharing and higher data quality, and availability
- Full implementation of uniform digital platform and electronic health records.
- Standardization of information included in electronic health records, regarding biomarkers and other relevant data [27].

• Data Protection and Ethical Consideration

Another facet of integration of personalized medicine in Serbia concerns data protection of electronic health records. These records should be used for decision making, as well as research (e.g., using anonymized data). Keeping in mind the sheer quantity of available patient data that may be subject to analysis in order to enable personalized diagnostics and treatments, implementation of precision medicine procedures in Serbia is, inter alia, contingent upon digitalization and streamlined medical data collection, processing, and sharing.

- Data protection laws, regulations, standards and policies that enable secure, efficient ethical and high-quality medical data collation and safe data sharing of individual molecular and other types of relevant information.

• Healthcare professionals' capacities and education

Personalized medicine in Serbia cannot be immediately introduced into the existing healthcare system. It requires the establishment of different mechanisms and educational programs that would provide healthcare professionals with an adequate understanding and a profound understanding of different aspects of personalized healthcare procedures and diagnostic techniques and skills needed for its full integration into the Serbian healthcare system. This probably necessitates functional and capacity analysis that will precisely define

skills needed to integrate personalized medicine and the introduction of personalized medicine in curricula of Serbian medical faculties. Newly obtained skills should not be strictly limited to narrow issues of personalized medicine but should also improve literacy in digital health and advanced use of health data.

Finally, the understanding of personalized medicine and its scope should not be limited to healthcare professionals. Other professionals in this multi-disciplinary field need to grasp their role in the next generation of medicine and healthcare.

- ### Patient education and awareness

Integration of personalized medicine in Serbia also requires the establishment of different patient-centric mechanisms and educational campaigns. The patient-centric health model implies a conscious effort towards the education of patients regarding the benefits and effects of personalized medicine. This information has to be accurate, readily available, and up to date. The promotion of personalized medicine diagnostic procedures and treatments in Serbian society may also be desirable. Policymakers and other stakeholders also need to educate patients regarding the possible effects of data collection during the provision of medical services.

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