PRECIZNO JAVNO ZDRAVLJE: DA LI JE POPULACIONI SKRINING GENOMA SMISLENA OPCIJA ZA RANO OTKRIVANJE RIZIKA OD ONKOLOŠKIH BOLESTI? RAZMATRANJA IZ SRBIJE

U FOKUSU

IN THE SPOTLIGHT

PRECISION PUBLIC HEALTH PERSPECTIVE: IS GENOMIC POPULATION SCREENING A VIABLE OPTION FOR THE EARLY DETECTION OF RISKS FOR ONCOLOGICAL DISEASES? REFLECTIONS FROM SERBIA

Bosiljka Đikanović[1,2], Janko Janković[1,2], Milena Čavić[3]

[1] Univerzitet u Beogradu, Medicinski fakultet, Institut za socijalnu medicinu, Beograd, Srbija

[2] Univerzitet u Beogradu, Medicinski fakultet, Centar – Škola javnog zdravlja i zdravstvenog menadžmenta, Beograd, Srbija

[3] Institut za onkologiju i radiologiju Srbije, Odeljenje za eksperimentalnu onkologiju, Beograd, Srbija

[1] *University of Belgrade, Faculty of Medicine, Institute of Social Medicine, Belgrade, Serbia*

[2] *University of Belgrade, Faculty of Medicine, Center - School of Public Health and Health Management, Belgrade, Serbia*

[3] *Institute for Oncology and Radiology of Serbia, Department of Experimental Oncology, Belgrade, Serbia*

SAŽETAK

Ovaj rad ima za cilj da objasni termin *precizno javno zdravlje* i njegovu primenu u ranom otkrivanju onkoloških bolesti i genomskih rizika za ove bolesti. Ukratko se razmatra upotreba veštačke inteligencije i profilisanje genoma, uključujući i uvide u trenutno stanje inovativnih pristupa u Republici Srbiji. Potrebno je stvoriti okruženje za skladištenje velikih genetičkih i zdravstvenih skupova podataka koje je zaštićeno i interoperabilno, u skladu sa principima nesmetanog pronalaženja, pristupačnosti, interoperabilnosti i ponovne upotrebe (engl. *findability, accessibility, interoperability, and reusability - FAIR*). Šira upotreba genomike u ranom otkrivanju rizika od onkoloških bolesti mora da ispuni dobro utvrđene kriterijume za populacioni skrining, što trenutno nije slučaj. Faktori rizika koji mogu da izazovu ispoljavanje gena dovodeći do onkoloških bolesti su dobro poznati, a to su: nezdravo okruženje uključujući zagađenje vazduha, pušenje i izloženost duvanskom dimu, stres, neuravnotežena ishrana i drugi štetni faktori. Stoga bi nadležne zdravstvene institucije i donosioci odluka u oblasti zdravstvene politike trebalo da se fokusiraju na izgradnju zdravog okruženja isto koliko i na rad na tehničkoj i tehnološkoj zdravstvenoj informacionoj infrastrukturi neophodnoj za dalji razvoj genomike i preciznog javnog zdravlja.

Ključne reči: precizno javno zdravlje, genomika, veštačka inteligencija, onkološke bolesti, skrining, zdravstvena politika

ABSTRACT

This paper aims to discuss the term *precision public health* and its application in the early detection of oncological diseases and genomic risks for these diseases. The use of artificial intelligence and genomic profiling are briefly elaborated on, including reflections on the current status of innovative approaches in the Republic of Serbia. An environment for big genetic and health data sets storage that is protected and interoperable needs to be created, in keeping with the findability, accessibility, interoperability, and reusability (FAIR) principles. Wider use of genomics in the early detection of risks for oncological diseases must meet the well-established criteria for population screening, which is currently not the case. The risk factors that can trigger the penetrance of genes, thus leading to oncological disease, are also well known, and are as follows: unhealthy environments including air pollution, smoking and exposure to second-hand smoke, stress, unbalanced diet, and other harmful factors. Therefore, health governance bodies and health policy decision-makers should focus on building a healthy environment as much as on working on the technical and technological health information infrastructure necessary for further development of genomics and precision public health.

Keywords: precision public health, genomics, artificial intelligence, oncological diseases, screening, health policy

Autor za korespondenciju:
Bosiljka Đikanović
Univerzitet u Beogradu, Medicinski fakultet
Institut za socijalnu medicinu i
Centar – Škola javnog zdravlja i zdravstvenog menadžmenta
Dr Subotića 8, 11000 Beograd, Srbija
Elektronska adresa: bosiljka.djikanovic@med.bg.ac.rs

Corresponding author:
Bosiljka Đikanovic
University of Belgrade, Faculty of Medicine
Institute of Social Medicine and
Center – School of Public Health and Health Management
8 Dr Subotića Street, 11000 Belgrade, Serbia
E-mail: bosiljka.djikanovic@med.bg.ac.rs

Primljeno • *Received*: February 28, 2025; **Revidirano • *Revised*:** March 18, 2025; **Prihvaćeno • *Accepted*:** March 21, 2025; ***Online first*:** March 31, 2025

DOI: 10.5937/smclk6-57145

MALIGNA OBOLJENJA U SRBIJI

Maligna oboljenja predstavljaju značajan javnozdravstveni problem u Republici Srbiji. Starosno standardizovana stopa incidencije (engl. *age-standardized incidence rate - ASIR*) iznosi 250,4 na 100.000 stanovnika [1], dok je stopa mortaliteta za sve tipove karcinoma u 2022. godini iznosila 128,4 na 100.000 stanovnika, što Srbiju svrstava na četvrto mesto u Evropi [2]. Nekoliko faktora rizika doprinosi ovoj nepovoljnoj statistici, kao što su: visoka prevalencija pušenja među odraslima (36,6%) [3], visok stepen zagađenosti vazduha tokom cele godine (prosečna godišnja koncentracija PM2,5 od 19,4 mg/m^3, u poređenju sa 14 mg/m^3 u evropskom regionu) [4], ishrana u kojoj su bogato zastupljene masti i prerađevine a koja je siromašna u vlaknima, ali i starenje stanovništva (2022. godine udeo osoba starosti 65 i više godina bio je 22,0%) [6], u kombinaciji sa niskom stopom ukupnog fertiliteta (1,63 u 2022. godini) [7].

Visoke incidencije malignih bolesti i mortaliteta uzrokovanog ovim bolestima su uočene još pre 20 godina, a nacionalni kreatori politike najavljivali su programe prevencije i ranog otkrivanja karcinoma kao strategiju koja je trebalo da poboljša dužinu i kvalitet života. Shodno tome, 2012. godine pokrenuti su programi skrininga populacije za tri vrste karcinoma: rak dojke (mamografija praćena biopsijom), karcinom grlića materice (Papa test praćen biopsijom), i kolorektalni test (test fekalne okultne krvi – engl. *fecal occult blood test - FOBT*, praćen kolonoskopijom i biopsijom) [8-10]. Iako je Nacionalna kancelarija za skrining raka, osnovana da koordiniše proaktivni pristup u pozivanju zdravog stanovništva (preciznije, stanovništva za koje se pretpostavlja da je zdravo) da se podvrgne skriningu, stope odgovora su ostale na skromnom nivou, daleko ispod željenih ciljeva. Uprkos svim naporima i sprovođenju javnozdravstvenih kampanja kako bi se podigla svest o značaju ranog otkrivanja karcinoma, prema *Serbia: Health System Review 2019*, stope odgovora su bile 11,4%, 15,8% i 5,0% ciljne populacije, za rak dojke, grlića materice i kolorektalnog kancera, što je daleko ispod stope odgovora u drugim evropskim zemljama [11-13].

Kao stručnjaci za javno zdravlje koji sagledavaju sveobuhvatnu i široku društvenu perspektivu, moramo da razmotrimo da li se inovativni pristupi dostupni u 21. veku mogu smisleno primeniti u ranom otkrivanju onkoloških bolesti i proceni rizika kod pretpostavljeno zdrave populacije. Štaviše, trebalo bi da ispitamo da li ovi pristupi u zdravstvenom domenu mogu da smanje stope mortaliteta i poboljšaju preživljavanje i kvalitet života.

INOVATIVNI PRISTUPI

Živimo u eri četvrte industrijske revolucije, a dostupnost inovativnih tehnologija, veštačke inteligencije (engl.

MALIGNANT DISEASES IN SERBIA

Malignant diseases are a significant public health problem in the Republic of Serbia. The age-standardized incidence rate (ASIR) is 250.4 per 100,000 population [1], while the mortality rate for all cancer types, in 2022, was 128.4 per 100,000 population, which puts Serbia in fourth place in Europe [2]. Several risk factors contribute to these unfavorable statistics, such as a high prevalence of smoking among adults (36.6%) [3], high levels of air pollution during the entire year (an annual average PM2.5 concentration of 19.4 μg/m^3, as compared to 14 μg/m^3 in the European Region) [4], a national diet rich in fat and processed foods and depleted in fiber [5], but also an aging population (in 2022, the share of persons aged 65 and over was 22.0%) [6], in combination with a low total fertility rate (1.63 in 2022) [7].

The threat of a high incidence of malignant diseases and mortality caused by these diseases was observed as early as 20 years ago, and national policymakers announced programs for the prevention and early detection of cancers as the strategy which was supposed to improve the length and quality of life. Consequently, population screening programs were launched for three types of cancers in 2012: breast cancer (mammography followed by biopsy), cervical cancer (Papa test followed by biopsy), and colorectal test (fecal occult blood test - FOBT, followed by colonoscopy and biopsy) [8-10]. Although the National Cancer Screening Office was established to coordinate a proactive approach in inviting the population believed to be healthy (ostensibly healthy) to undergo screening, the response rates remained modest, far below the desired goals. Despite all efforts and the implementation of public health campaigns to raise awareness of the importance of early detection of cancers, according to *Serbia: Health System Review 2019*, the response rates were 11.4%, 15.8%, and 5.0% of the target population, for breast, cervical and colorectal cancer, respectively, which was far below the reported response rates for other European countries [11-13].

As public health professionals with a comprehensive societal perspective, we must consider whether the innovative approaches available in the 21st century can meaningfully be used in the early detection of oncological diseases and the assessment of risks within ostensibly healthy populations. Furthermore, we should examine whether these approaches can reduce mortality rates and enhance survival and health-related quality of life.

INNOVATIVE APPROACHES

We are living in the era of the fourth industrial revolution, and the availability of innovative technologies,

artificial intelligence – AI) i profilisanja genoma imaju revolucionaran uticaj na sve aspekte zdravstvene zaštite. Stoga se postavlja validno i opravdano pitanje: da li ovi inovativni pristupi mogu da unaprede rano otkrivanje i lečenje onkoloških bolesti? Dok aspekt onkoloških bolesti u vezi sa inovativnim dijagnostičkim metodama i terapijama ostavljamo na razmatranje kliničarima, patolozima i specijalistima molekularne biologije, mi možemo da razmotrimo prvi deo, odnosno rano otkrivanje onkoloških bolesti. U toku su inicijative i projekti programiranja *AI* modela koji će se koristiti u radiologiji za validno otkrivanje sumnjivih promena, posebno kod čitanje izveštaja sa mamografije [14-17]. Nekoliko studija je dokazalo da korišćenje veštačke inteligencije u prvom čitanju radioloških izveštaja može biti efikasno i isplativo. Može da prevaziđe važnu barijeru, kao što je nedostatak visoko kvalifikovanih radiologa, što je poznato kao jedno od najvažnijih uskih grla u zdravstvenim sistemima širom sveta. Ovo je posebno slučaj u zemljama u razvoju, zbog odliva mozgova i zbog opsežne obuke koju lekari moraju da prođu pre nego što postanu specijalisti [18]. Međutim, iako se u retrospektivnim evaluacijama pokazalo da *AI* obećava u domenu skrininga putem mamografije, malo je prospektivnih studija na ovu temu, zbog čega je obim primene veštačke inteligencije još uvek ograničen [19]. Očekuje se da bi u budućnosti veštačka inteligencija mogla da doprinese ranom otkrivanju klinički relevantnih karcinoma i da na taj način smanji obim posla u čitanju snimaka, a bez povećanja broja lažnih pozitivnih rezultata [20].

Osim veštačke inteligencije, drugi inovativni pristup koji bismo želeli da razmotrimo jeste upotreba genomike. Zahvaljujući naprednim tehnikama za profilisanje genoma, kao što je sekvenciranje sledeće generacije (engl. *next generation sequencing - NGS*), analize genoma obolelih tkiva su danas skoro neizbežni deo profilisanja tumora, što omogućava propisivanje najefikasnijih personalizovanih terapija koje ciljaju biomolekule odgovorne za razvoj raka [21]. Međutim, dostupnost sekvenciranja sledeće generacije (*NGS*) i inovativnih terapija zavisi od finansijskih sredstava zdravstvenog sistema, i identifikovani su različiti modeli za finansiranje ovih pristupa [22,23].

Pomenuti inovativni pristupi nisu nepoznati u Srbiji. Na nacionalnom nivou mapirano je trinaest organizacija opremljenih za *NGS*. Sve ove organizacije su u javnom vlasništvu, a njihovi sistemi sekvenciranja su različitih proizvođača (*Illumina, BGI, Okford Nanopore Technologies, Thermo Fisher Scientific, PacBio*) [24]. Dostupnost inovativnih terapija se takođe povećava. Prema poslednjim podacima, Fond za zdravstveno osiguranje Republike Srbije finansira 17 inovativnih terapija za onkološke bolesti, a ukupni izdaci za njih su u 2024.

artificial intelligence (AI), and genome profiling are making a revolutionary difference in all aspects of health care. Therefore, there is a valid and justified question: can these innovative approaches improve the early detection and treatment of oncological diseases? While we leave the aspect of oncological diseases related to innovative diagnostic methods and therapies to the consideration of clinicians, pathologists, and molecular biology specialists, let us consider the first part, i.e., the early detection of oncological diseases. There are ongoing efforts and projects related to training AI models to be used in radiology for the valid detection of suspicious changes/lesions, particularly for reading mammography reports [14-17]. Several studies have proven that using AI in the first reading of radiology reports can be efficient and cost-effective. It can overcome an important barrier, such as the lack of highly qualified radiologists, known as one of the biggest bottlenecks in the healthcare systems worldwide. This is especially the case in developing countries, due to brain drain and because of the extensive training that doctors have to undergo before becoming specialists [18]. However, although AI has shown promise in mammography-based screening in retrospective evaluations, few prospective studies exist, which is why the scope of its application is still limited [19]. It is expected that in the future, AI might contribute to the early detection of clinically relevant cancers thus reducing the screen-reading workload without increasing false positives [20].

Apart from AI, the other innovative approach we would like to consider is the use of genomics. Thanks to the advanced techniques for genome profiling, one of which is known as Next Generation Sequencing (NGS), genomic analyses of diseased tissues are nowadays an almost inevitable part of tumor profiling, which leads to prescribing the most effective personalized treatments that target biomolecules responsible for cancer development [21]. However, the availability of NGS and innovative therapies depends on the financial resources of the healthcare system, and there are different models for securing funding for these approaches [22,23].

The aforementioned innovative approaches are not unknown in Serbia. At the national level, thirteen organizations equipped to perform NGS have been mapped. Their sequencing systems are from different manufacturers (Illumina, BGI, Oxford Nanopore Technologies, Thermo Fisher Scientific, PacBio). All of these organizations are publicly owned [24]. The availability of innovative therapies is also increasing. According to recent announcements, the National Health Insurance Fund of the Republic of Serbia is financing 17 innovative therapies for oncological diseases, and the overall

godini iznosili 18,5 milijardi dinara, što je skoro 157 miliona evra [25].

PRECIZNA MEDICINA I PRECIZNO JAVNO ZDRAVLJE

U proteklih 20 godina, zbog dostupnosti sekvenciranja sledeće generacije, koje omogućava znatno brže i jeftinije analize ljudskog genoma, pojam precizne medicine (koji se načelno smatra analognim sa pojmom personalizovane medicine) evoluirao je tako da u donošenje kliničkih odluka uključi i profilisanje genoma. Iako ne postoji univerzalno prihvaćena definicija personalizovane medicine, savetodavna grupa programa Horizont 2020 je definiše kao „medicinski model u kojem se koristi karakterizacija fenotipova i genotipova pojedinaca (npr. molekularno profilisanje, medicinsko snimanje, podaci o životnom stilu) u cilju pravovremenog prilagođavanja terapeutske strategije osobi i/ili utvrđivanja predispozicija za bolest i/ili pravovremene i ciljane prevencije". Pristup lečenju raka po „univerzalnom" principu postepeno je zamenjen prilagođavanjem terapije svakom pojedinačnom pacijentu, što je postavilo nove izazove pred kliničare i zdravstvene sisteme. Međutim, uspešna precizna medicina zahteva populacionu perspektivu, čime se utire put ka uspostavljanju koncepta preciznog javnog zdravlja (engl. *precision public health – PPH*) [21]. Precizno javno zdravlje može se definisati kao „sredstvo za poboljšanje zdravlja stanovništva primenom novih tehnologija, posebno genomike i digitalnih tehnologija, koje bi usmeravale praksu javnog zdravlja generisanjem više individualno prilagođenih oblika delovanja i politika" [26]. Drugim rečima, *PPH* se odnosi na obezbeđivanje „pravog oblika delovanja, pravoj populaciji, u pravo vreme" [27], odnosno na korišćenje najboljih dostupnih podataka za efikasnije i delotvornije ciljano delovanje ka onima kojima je to potrebno [28]. Dva najveća pokretača u *PPH* su istraživanje genoma i zdravstvene informacione tehnologije koje prikupljaju podatke u vezi sa zdravljem u mašinski čitljivom obliku, zahvaljujući interoperabilnosti zdravstvenih informacionih sistema. Stručnjaci za zdravstvene sisteme, profesionalci u oblasti javnog zdravlja i donosioci odluka treba da razumeju inovativne, digitalne i „omika" tehnologije (poslednje se odnosi na sufiks koji se javlja u rečima genomika, epigenomika, proteomika, metabolomika i metagenomika). Ove tehnologije nisu cilj same po sebi, već alati za promovisanje zdravlja i prevenciju bolesti, ukoliko se primenjuju razumno i odgovorno, odnosno ako ih prate odgovarajuće strategije upravljanja rizicima, kao što su savetovanje i nadzor. Ipak, da bi se opravdala njihova upotreba u širim razmerama potrebno je pozabaviti se i mnogim drugim metodološkim pitanjima i nedoumicama, što je posebno relevantno kod

expenditure for them was 18.5 billion dinars in 2024, which is almost 157 million euros [25].

PRECISION MEDICINE AND PRECISION PUBLIC HEALTH

In the past 20 years, due to the availability of NGS, which enables significantly faster and cheaper analyses of the human genome, the concept of precision medicine (generally considered analogous to personalized medicine) evolved to include genetic profiling in clinical decision-making. Although there is no universally accepted definition of personalized medicine, the Horizon 2020 Advisory Group defines it as "a medical model using characterization of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention". The "one size fits all" approach to cancer treatment was gradually replaced by tailoring treatments to each individual, which has placed new challenges before clinicians and healthcare systems. However, successful precision medicine requires a population perspective, paving the way to establishing the precision public health (PPH) concept [21]. Precision public health can be defined as "a means of improving population health through the use of new technologies, particularly genomics and digital, which would guide public health practice by generating more individually tailored interventions and policies" [26]. In other words, PPH is about delivering "the right intervention, at the right time, to the right population" [27], or using the best available data to more effectively and efficiently target those in need [28]. The two biggest drivers in PPH are genomic research and health information technologies that collect health-related data in a machine-readable form, owing to the interoperability of health information systems. However, specialists in health systems, decision-makers, and public health professionals need to understand innovative, digital, and "omics" technologies (the latter is the suffix that applies to genomics, epigenomics, proteomics, metabolomics, and metagenomics). They are not the goal in themselves, but tools for health promotion and disease prevention, if applied reasonably and responsibly, i.e., if followed by appropriate risk management strategies such as counseling and surveillance. Still, many methodological considerations and concerns remain to be addressed in order to justify their use on a large scale, which is particularly relevant in their use for population genomic screening to identify risk factors for malignant diseases [26,29].

njihove upotrebe u populacionom skriningu genoma za identifikaciju faktora rizika za maligne bolesti [26,29].

GENOMIKA U SVETU I SRBIJI

Profilisanje genoma pojedinačnih pacijenata i opšte populacije danas je predmet istraživanja koja se sprovode širom sveta, uglavnom u razvijenim, ali i u zemljama u razvoju [21,30]. Na primer, kompanija *Genomics England* je pokrenula inicijativu pod nazivom „Projekat 100.000 genoma" (engl. *100,000 Genomes Project*) sa ciljem da se sekvencira 100.000 genoma za oko 85.000 pacijenata registrovanih u njihovoj Nacionalnoj zdravstvenoj službi (engl. *National Health Service – NHS*), koji boluju od raka ili retkih bolesti, dok je Evropska unija pokrenula inicijativu „1+ milion genoma" (engl. *1+ Million Genomes – 1+MG*), koja ima za cilj da obezbedi identifikovanje genomskog profila i pristup pratećim kliničkim podacima širom Evrope [31,32]. Projekat „Genom Evrope" (engl. *Genome of Europe*) ima za cilj da izgradi evropsku mrežu nacionalnih genomskih referentnih kohorti za prikupljanje podataka o genetskom sastavu i zdravih i bolesnih osoba (sekvencirani genomi) [33].

U Srbiji su uloženi različiti napori kako bi se potencijal genetičkih podataka iskoristio na dobrobit pacijenata i građana, ali su oni uglavnom fragmentirani i predstavljaju pojedinačne institucionalne aktivnosti [34]. Međutim, od novembra 2023. godine, u cilju fokusiranijeg delovanja na nacionalnom nivou, Srbija je postala i deo inicijative/konzorcijuma „Genom Evrope", zajedno sa 29 zemalja Evropske unije (EU), i svega tri zemlje izvan EU (pored Srbije, još i Turska i Norveška) [33,35]. Očekuje se da će dobijeni nalazi dovesti do revolucionarnog uvida u genetsku strukturu, omogućavajući „personalizovane zdravstvene tretmane sa potencijalom da se unapredi prevencija bolesti" [32].

U Srbiji su mapirani kapaciteti za sprovođenje analiza genoma i čini se da naša zemlja ima realan potencijal i volju da prati svetske trendove u ovoj oblasti [24,35]. Međutim, ostaju određeni izazovi, koji se, između ostalog, odnose i na nedostatak kvalifikovanog istraživačkog i medicinskog osoblja za analizu i tumačenje rezultata sekvenciranja. Da bi se rešilo ovo pitanje, Ministarstvo prosvete je 2025. godine pokrenulo prvi master program bioinformatike (*Master 4.0 Bioinformatika*) za obuku sledeće generacije studenata za bioinformatiku, genomiku, molekularnu biologiju, analizu kliničkih podataka, farmakogenetiku, primenu veštačke inteligencije u biologiji i medicini, kao i za analizu velikih podataka [36]. Takođe, u Srbiji je, na nacionalnom nivou, koncipirana studija za dobrovoljno profilisanje genoma među 1.000 osoba starosti 18-40 godina, iz opšte (zdrave) populacije [37]. Studija treba da bude praćena uspostavljanjem Registra genetičkih i biomedicinskih

GENOMICS IN THE WORLD AND SERBIA

Numerous projects and ongoing initiatives related to genomic profiling in patients and the general population are nowadays being applied worldwide, mostly in developed but also in developing countries [21,30]. For example, Genomics England launched an initiative called "100,000 Genomes Project" aiming to sequence 100,000 genomes from around 85,000 patients registered with their National Health Service (NHS), who are suffering from either cancer or a rare disease, while the European Union announced "1+ Million Genomes" (1+MG), an initiative aiming to secure access to genomics and the corresponding clinical data across Europe [31,32]. The "Genome of Europe" project aims to build a European network of national genomic reference cohorts to collect data on the genetic composition of both healthy and diseased individuals (sequenced genomes) [33].

In Serbia, various efforts have been implemented to use the power of genetic data for improvements in the well-being of citizens, but they are mostly fragmented and represent unrelated institutional activities [34]. Since November 2023, as a more focused national effort, Serbia has also become a part of the "Genome of Europe" initiative/consortium, together with 29 European Union (EU) countries and only three countries outside the EU (besides Serbia, also Turkey and Norway) [33,35]. These findings are expected to lead to groundbreaking insights into genetic structure, enabling "personalized healthcare treatments with the potential to improve disease prevention" [32].

Capacities for genomic analyses have been mapped in Serbia, and it seems that the country has reasonable potential and willingness to keep up with the global trends in this domain [24,35]. However, certain challenges remain, particularly the lack of qualified research and medical staff for analyzing and interpreting sequencing results. To address this issue, in 2025, the Ministry of Education launched the first Bioinformatics Master's Program to train the next generation of students in bioinformatics, genomics, molecular biology, clinical data analysis, pharmacogenetics, the application of artificial intelligence in biology and medicine, as well as in big data analysis [36]. At the national level, a study on voluntary genomic profiling among 1,000 individuals 18-40 years old, from the general (healthy) population, is being conceptualized [37]. This needs to be followed by the project of establishing a Genetic and Biomedical Data Registry, i.e., an information system for storing and exchanging genetic data under the highest technical and security standards, for research and development purposes in biotechnology, healthcare, and genetics

podataka, odnosno informacionog sistema za čuvanje i razmenu genetičkih podataka po najvišim tehničkim i bezbednosnim standardima, za potrebe istraživanja i razvoja u biotehnologiji, zdravstvu i genetici [37]. Ove aktivnosti predstavljaju veliki podsticaj i priliku za dalji razvoj u korak sa svetom, ali i veliku odgovornost za obezbeđivanje najdelotvornijih intervencija za osobe sa identifikovanim genomskim rizicima.

MOGUĆNOSTI GENOMIKE U POPULACIONIM SKRININZIMA NA MALIGNA OBOLJENJA

Prema smernicama Američkog koledža za medicinsku genetiku i genomiku (engl. *American College of Medical Genetics and Genomics - ACMG*) i uslovima iz prve kategorije koje je definisao Centar za kontrolu bolesti i prevenciju (engl. *Centers for Disease Control and Prevention – CDC*) Sjedinjenih Američkih Država, najčešća i preporučena primena populacionog skrininga genoma jeste u cilju identifikovanja genskih mutacija koje predisponiraju pojedinca na jedno od sledećih stanja: nasledni sindrom dojke i jajnika (engl. *hereditary breast and ovarian cancer syndrome - HBOC*), koji predstavlja rizik za oboljevanje od karcinoma dojke, jajnika, jajovoda, peritoneuma i drugih karcinoma usled mutacija gena raka dojke 1 (engl. *breast cancer gene 1 – BRCA1*) ili gena raka dojke 2 (engl. *breast cancer gene 2 – BRCA2*), i Linčov sindrom (engl. *Lynch syndrome – LS*), koji predstavlja povećani rizik za oboljevanje od kolorektalnog, endometrijalnog, raka jajnika i drugih karcinoma [30,38].

Poznato je da mutacije gena *BRCA1* i *BRCA2* imaju relativno visoku penetrantnost: u meta-analizi koju su sproveli Čen i Parmiđani utvrđen je kumulativni rizik od raka dojke među nosiocima mutacija pri starosti od 70 godina od 57% za BRCA1 (95% interval poverenja (*CI*) 47%-66%) i 49% za *BRCA2* (95% *CI*, 40%-57%), a bio je još niži za rak jajnika (40% i 18% za *BRCA1* i *BRCA2*, 95% *CI* 35%-46% i 95% *CI* 13%-23%) [39]. Sa druge strane, prevalencija *BRCA* mutacija među pacijentkinjama sa rakom dojke kreće se u rasponu od 1,8% u Španiji do 36,9% u Sjedinjenim Državama, prema sistematskom pregledu 70 studija širom sveta koji su sproveli Armstrong i saradnici [40]. U nordijskim zemljama utvrđeno je da je naslednost raka dojke kod žena 31%, dok je kod kolorektalnog karcinoma 15% [41]. U Srbiji se na nacionalnom nivou, na Institutu za onkologiju i radiologiju Srbije, izvodi testiranje na prisustvo germinativnih mutacija u genima koji ukazuju na predispoziciju za nasledni rak dojke i jajnika i Linčov sindrom. Utvrđeno je da su najčešće mutacije kod raka dojke i jajnika na *BRCA1* (7,6%), *BRCA2* (4,8%), genu partneru i lokalizatoru *BRCA2* (engl. *partner and localizer of BRCA2 gene - PALB2*) (4,1%) i genu kinaza 2 kontrolne tačke (engl. *checkpoint kinase 2 gene - CHEK2*) (3,8%) [42]. Identi-

[37]. These activities represent a great incentive and opportunity, but also a great responsibility to deliver the most cost-effective interventions to persons with identified genomic risks.

THE POTENTIAL OF GENOMICS IN POPULATION SCREENING ASSOCIATED WITH MALIGNANT DISEASES

According to the American College of Medical Genetics and Genomics (ACMG) and the United States Centers for Disease Control and Prevention (CDC) Tier 1 conditions, the most common and recommended application of population genetic screening is for the identification of genetic mutations that predispose an individual to one of the following conditions: hereditary breast and ovarian cancer syndrome (HBOC), which presents a risk for breast, ovarian, tubal, peritoneal and other cancers due to mutations in breast cancer gene 1 (BRCA1) or breast cancer gene 2 (BRCA2), and Lynch syndrome (LS), which represents an increased risk for colorectal, endometrial, ovarian and other cancers [30,38].

Mutations of the BRCA1 and BRCA2 genes are known for having relatively high penetrance: the cumulative risk for breast cancer among mutation carriers at the age of 70 was 57% for BRCA1 (95% confidence interval (CI) 47%-66%) and 49% for BRCA2 (95% CI 40%-57%), and even lower for ovarian cancer (40% and 18% for BRCA1 and BRCA2 respectively, 95% CI 35%-46% and 95% CI 13%-23%), as found in a meta-analysis conducted by Chen and Parmigiani [39]. On the other hand, the prevalence of BRCA mutations among patients with breast cancers is in the range of 1.8% in Spain to 36.9% in the United States, according to the systematic review of 70 studies worldwide conducted by Armstrong et al. [40]. In Nordic countries, the heritability of female breast cancer was found to be 31%, while for colorectal cancer it was found to be 15% [41]. In Serbia, testing for germline mutations in cancer susceptibility genes for hereditary breast and ovarian cancer and Lynch syndrome is performed at the national level, at the Institute for Oncology and Radiology of Serbia. The most frequent mutations in breast and ovarian cancer were found to be in BRCA1 (7.6%), BRCA2 (4.8%), the partner and localizer of BRCA2 gene (PALB2) (4.1%), and the checkpoint kinase 2 gene (CHEK2) (3.8%) [42]. Identifying pathogenic and likely pathogenic variants in genes that carry a high predisposition for hereditary cancers allows for the stratification of families by risk and has become a widely accepted global practice.

It is important to note that if an individual is a carrier of the aforementioned genetic mutations, this does not necessarily mean that this person is unhealthy or will be unhealthy. This is, obviously, a matter of prob-

fikovanje patogenih i verovatnih patogenih varijanti u genima koji daju visoku predispoziciju za nasledne karcinome omogućava stratifikaciju porodica prema riziku i preraslo je u široko prihvaćenu globalnu praksu.

Važno je napomenuti da ako je osoba nosilac pomenutih genskih mutacija, to ne mora da znači da je ona automatski bolesna ili da će se razboleti. Ovo je, očigledno, pitanje verovatnoće koja se može modifikovati. Dobro je poznato da se bolest javlja kao interakcija između genetskih i ekoloških faktora rizika, kao što su izloženost stresu, nepovoljni uslovi životne sredine, zagađenje vazduha, nezdrav stil života (npr. pušenje, nedostatak fizičke aktivnosti, nezdrava ishrana), ali kako se tačno bolest razvija i šta i kada pokreće ispoljavanje genskih mutacija, odnosno pojavu novih mutacija i ispoljavanje bolesti, ostaje nerazjašnjeno. Osim genetike, potrebno je više informacija iz longitudinalnih studija o izloženosti faktorima rizika tokom života da bi se izgradilo znanje o prirodnom toku bolesti. Digitalne zdravstvene informacije mogu pomoći u individualnom prikupljanju podataka, dok je veštačka inteligencija korisna u analizi velikih baza podataka (engl. *big data*) i identifikovanju obrazaca i povezanosti između individualnih životnih iskustava, izloženosti i zdravstvenih ishoda. Međutim, kada se onkološka bolest na kraju desi, svaki tumor ima svoju genetiku, što se može dokazati pomoću sekvenciranja sledeće generacije (*NGS*) i genomskih analiza, a dostupne su i inovativne terapije za prevazilaženje genskih mutacija kao osnovnog uzroka maligne bolesti, što je predstavlja osnovu precizne medicine.

SOCIJALNI, PRAVNI I ETIČKI ASPEKTI

Imajući u vidu sve prethodno opisane činjenice, ne možemo a da se ne zapitamo: koja je korist ili dodatna vrednost poznavanja našeg genetskog statusa kada smo zdravi? Kako to utiče na naše izglede da dobijemo određenu onkološku bolest, verovatnoću preživaljavanja ukoliko se razbolimo ili kvalitet života povezan sa zdravljem? Trenutno, odgovor nedostaje, kao i saznanja o prirodnom toku bolesti [43]. Da li bi informacije o genetskom statusu povećale odziv pojedinca na redovne preglede i poboljšale izbore zdravog načina života? Ova i mnoga druga pitanja treba pažljivo razmotriti, a odgovor sigurno nije uniforman [44]. Iako nema sumnje da upotreba genomskih podataka ima značajan potencijal za preciznu medicinu, neophodna su posebna razmatranja kako bi se ove informacije koristile etički, odgovorno, svrsishodno i bezbedno, bez potencijalne zloupotrebe ili štete [45].

Potencijalno, informacija da je zdrava osoba nosilac genske mutacije može da ima neke prednosti, kao što je povećana motivacija za redovno praćenje svog zdravstvenog stanja i uzdržavanje od izlaganja faktorima rizika

ability which can be modified. It is well known that disease appears as an interaction between genetic and environmental risk factors. These risk factors include exposure to stress, unfavorable environmental conditions, such as air pollution, and unhealthy lifestyles (e.g., smoking, lack of physical activity, and unhealthy nutrition), but how exactly the disease develops and what and when triggers the penetrance of gene mutations, or the appearance of new ones and the expression of disease, remains unclear. More information is needed from longitudinal studies on lifetime exposure to risk factors, in addition to genetics, to build knowledge on the natural course of disease. Digital health information might help in individual data collection, while AI is useful in the analysis of big data and identification of patterns and associations between individual lifetime experiences, exposures, and health outcomes. However, when oncological disease eventually happens, each tumor has its own genetics, which can be proven by NGS and genomic analyses, and innovative therapies are available to address the genetic mutations as the root cause of malignant disease, which is the foundation of precision medicine.

SOCIAL, LEGAL, AND ETHICAL CONSIDERATIONS

Bearing all the previously described facts in mind, we cannot but ask ourselves: what are the benefits or the added value of knowing our genetic status when we are healthy? How does it affect our chances of getting a particular oncological disease, our survival, or our health-related quality of life? Currently, the answer is lacking, as is the knowledge related to the natural course of disease [43]. Would the information on genetic status increase an individual's compliance with regular checkups and improve healthy lifestyle choices? These and many other questions need to be carefully considered, and the answers to these questions are by no means uniform [44]. Although there is no doubt that the use of genomic data holds significant potential for precision medicine, special considerations are necessary in order to use this information ethically, responsibly, safely, and beneficially, without potential harm or misuse [45].

Potentially, the information that a person is a carrier of a gene mutation might have some advantages, such as increased motivation for regular monitoring of their health status and refraining from being exposed to behavioral risk factors that are under individual control. At the same time, this information could cause fear and anxiety. Furthermore, risk factors originating from the environment are public responsibility, and

u kontekstu određenih ponašanja koja su pod individualnom kontrolom. Istovremeno, ove informacije mogu da izazovu strah i anksioznost. Štaviše, faktori rizika koji potiču iz životne sredine su javna odgovornost, a države i vlade moraju da obezbede kako donošenje, tako i primenu odgovarajućih i preporučenih politika koje se odnose na stvaranje zdrave životne sredine. Najbolji negativan primer za to u Republici Srbiji je Strategija kontrole duvana koja je potpisana i ratifikovana pre skoro 20 godina i propraćena donošenjem niza zakonskih i podzakonskih akata koji su, između ostalog, predviđali kreiranje javnih prostora bez duvanskog dima. Međutim, pušenje u zatvorenim prostorima mnogih ugostiteljskih objekata (a samim tim i pasivno izlaganje duvanskom dimu) u Srbiji danas još uvek nije zabranjeno, što znači da su ljudi u velikoj meri izloženi pasivnom pušenju. Pušenje je direktni faktor rizika za sva onkološka oboljenja, prevashodno za rak pluća, čiji je *ASIR* 2022. godine iznosio 40,4 na 100.000 stanovnika, što je Srbiju svrstalo na četvrto mesto u svetu (ispred Srbije su Mađarska, Kina i Nova Kaledonija) [46].

Informacija o tome da je neko nosilac genske mutacije sa relativno visokim potencijalom da se razvije u onkološku bolest može imati značajan negativan uticaj na nečije psihičko blagostanje, posebno ako se ne saopšti pravilno. Efekat koji ova informacija može da ima na članove porodice nosilaca patogenih mutacija je takođe aspekt koji treba uzeti u obzir. Dobra praksa predlaže savetovanje pre i posle genomskog testiranja i adekvatno upravljanje rizikom od bolesti [47]. Bez ovih resursa, bilo bi neodgovorno ostaviti pojedince da samoinicijativno i bez profesionalne podrške realizuju genomsko testiranje, u bilo kom okruženju. U razvijenijim sredinama postoje neke ideje i projekti koji se odnose na promovisanje testiranja genoma u primarnoj zdravstvenoj zaštiti [48,49]. Da bi bili uspešni i da ne bi naneli štetu, ovi projekti moraju da budu udruženi sa složenom infrastrukturom koja omogućava preventivne intervencije i kvalitetnu komunikaciju između pružaoca usluga i pojedinaca/pacijenata, obezbeđujući da se prednosti dobro razumeju i da strategije za upravljanje rizikom budu postavljene nakon dobijanja rezultata testiranja.

Kriterijumi za sprovođenje bilo koje vrste populacionog skrininga ustanovljeni su još 1968. godine, i testiranje genoma radi otkrivanja gena povezanih sa rizikom za malignim oboljenjima kod zdrave populacije nisu u tom smislu izuzetak [50,51]. Kriterijumi se odnose na dostupnost odgovarajućeg skrining testa, koji mora biti dovoljno osetljiv i specifičan, dostupan po niskoj ceni, lak za primenu, prihvatljiv, neinvazivan, bezbedan, udoban i isplativ. Većinu ovih kriterijuma moglo bi da ispuni sekvenciranje sledeće generacije kao alat za skrining, pri čemu je još uvek upitna njegova isplativost,

governments and societies have to ensure that appropriate and recommended policies related to building a healthy environment are launched and applied. The best negative example of this in the Republic of Serbia is the tobacco control strategy that was signed and ratified almost 20 years ago, followed by a set of national legislation that envisaged creating smoking-free public spaces, among other initiatives. However, nowadays, indoor smoking (and therefore passive exposure) in Serbia is still not banned in many restaurants and cafes, which means that people are greatly exposed to second-hand smoke. This is a direct risk factor for all oncological diseases, primarily lung cancer, whose ASIR was 40.4 per 100,000 population in 2022, which put Serbia in fourth place globally, preceded by Hungary, China, and New Caledonia [46].

Being aware of the fact that one is a carrier of a gene mutation with a relatively high penetrance potential to develop oncological disease may have a considerable negative impact on one's psychological well-being, especially if not communicated properly. The effect it has on family members of pathogenic mutation carriers is also an aspect to be considered. Good practice proposes counseling before and after genomic testing and adequate disease risk management [47]. Without these resources in place, it would be irresponsible to leave individuals to deal with genomic testing themselves, in any setting. In more developed environments, there are some ideas and projects related to promoting genomic testing in primary healthcare services [48,49]. To be successful and do no harm, these projects have to be followed by complex infrastructure that enables preventive interventions and high-quality communication between providers and individuals/patients, assuring that advantages are well understood and strategies for risk management are in place after receiving test results.

Criteria for any kind of population screening were established in 1968, and genomic testing for detecting genes associated with malignant diseases in healthy populations is no exception [50,51]. Criteria are related to the availability of an appropriate screening test, which has to be sufficiently sensitive and specific, available at a low cost, easy to apply, acceptable, non-invasive, safe, comfortable, and cost-effective. The majority of these criteria could be met by NGS as a screening tool, with cost-effectiveness still being debated, even in simulated cohorts with modeled expected outcomes, such as incidence and quality-adjusted life years (QALY) after survival [52-54].

The other criterion for population screening is the availability of effective interventions that make a difference in survival and QALY. Basically, in the case

čak i u istraživanjima na simuliranim kohortama i modelovanim očekivanim ishodima kao što su incidencija i godine života prilagođene za kvalitet (engl. *quality-adjusted life years - QALY*) nakon preživljavanja [52-54].

Drugi kriterijum za populacioni skrining je dostupnost delotvornih intervencija koje utiču na preživljavanje i *QALY,* a nakon identifikovanog prisustva rizika. U principu, kada su u pitanju „omika" markeri rizika za onkološke bolesti, te delotvorne intervencije nisu ništa drugo do tradicionalne intervencije promocije javnog zdravlja i prevencije, koje su se pokazale kao strategije koje obezbeđuju najbolji rezultat naspram ulaganja. To su mere kontrole duvana, delovanje u smislu smanjenja zagađenja vazduha i promocije zdravih stilova života, ali i programi za rano otkrivanje kliničkih bolesti tradicionalnim skrining instrumentima sa dovoljnim nivoom osetljivosti (sposobnost da se pravilno identifikuju slučajevi bolesti tj. tačno pozitivni slučajevi) i specifičnosti (sposobnost da se pravilno identifikuju pojedinci koji su bez bolesti, odnosno tačno negativni slučajevi). Ovo nas vraća na početak pristupa kontroli onkoloških bolesti, odnosno na potrebu da se pošalje poruka da bez „staromodnih" individualnih i populacionih mera koje su optimizovane i uspostavljene na nivou društva, ne možemo očekivati da rano otkrivanje genomskih faktora rizika može poboljšati preživljavanje i *QALY* u slučajevima poznatih genetskih stanja kao što su *HBOC* i Linčov sindrom. Čak i kada se skrining genskog panela za ova stanja obavlja kao lični izbor, obično od strane onih koji mogu to da priušte ili su visoko motivisani da preduzmu testiranje genoma, iste mere za promociju zdravlja i prevenciju bolesti treba da budu dostupne i pristupačne, i na individualnom i na populacionom nivou. Javnozdravstvene mere utiču na sve i trebalo bi da svakako postoje (kao što je stvaranje okruženja bez duvana, na primer), dok individualne mere promocije zdravlja (zdravi stilovi života, na primer) zavise od prihoda i socioekonomskog statusa pojedinca, te bi ukupni odgovor na rezultate genetičkog testiranja mogao da poveća zdravstvene nejednakosti [55].

IMPLIKACIJE U DOMENU ZDRAVSTVENE POLITIKE

Javnozdravstvene mere, promocija zdravlja i prevencija usmerena na dobro poznate faktore rizika za onkološke bolesti nisu izgubile na značaju, niti su ih umanjile mogućnosti koje pružaju genomika i veštačka inteligencija [56]. Nadležne zdravstvene institucije i donosioci odluka u oblasti zdravstvene politike trebalo bi da se fokusiraju na izgradnju zdravog okruženja isto koliko i na rad na tehničkoj i tehnološkoj zdravstvenoj informacionoj infrastrukturi neophodnoj za dalji razvoj genomike i preciznog javnog zdravlja [57,58]. Potreb-

of "omics" markers of risks for oncological disease, these interventions are just traditional public health promotion and prevention interventions, which have proven to be "best-buy" strategies. These are tobacco control measures, efforts related to the decrease of air pollution, and promotion of healthy lifestyles, but also programs for early detection of clinical diseases by traditional screening instruments with sufficient levels of sensitivity (ability to correctly identify cases of disease) and specificity (ability to correctly identify individuals who are disease free, i.e. true negative cases). This brings us back to the beginning, i.e., sending the message that without "old fashioned" individual and population measures, optimized and in place, we cannot expect robust evidence that early detection of genomic risk factors can improve survival and QALY in cases of known actionable genetic conditions such HBOC, and Lynch syndrome. Even when gene panel screenings for these conditions are performed as a personal choice, typically by those who can afford or are highly motivated to pursue genomic testing, the same individual and public health promotion and prevention measures should be available and accessible. Public health measures affect everyone and should already be in place (such as creating tobacco-free environments, for example), while individual health promotion measures (healthy lifestyles, for example) depend on the income and socio-economic status of an individual. Therefore, the overall response to the results of genetic testing might increase health inequalities [55].

POLICY IMPLICATIONS

Public health measures, health promotion, and prevention related to well-known risk factors for oncological diseases did not lose their importance, and innovations such as genomics and artificial intelligence did not decrease their significance either [56]. Health governance bodies and health policy decision-makers should focus on building a healthy environment as much as on working on the technical and technological health information infrastructure necessary for further development of genomics and precision public health [57,58]. An environment for big genetic and health data sets storage that is protected and interoperable according to FAIR (findability, accessibility, interoperability, and reusability) principles needs to be created [59]. Leveraging biomedical research and development in Serbia is associated with creating a national register of genomics and health data, as a great national step forward towards the health promotion of our citizens, through precision medicine and precision public health.

no je stvoriti okruženje za skladištenje velikih genetičkih i zdravstvenih skupova podataka koje je zaštićeno i interoperabilno, u skladu sa principima nesmetanog pronalaženja, pristupačnosti, interoperabilnosti i ponovne upotrebe (engl. *findability, accessibility, interoperability, and reusability - FAIR*). [59]. Puna primena i dalji razvoj biomedicinskih istraživanja u Srbiji su u velikoj meri povezani sa formiranjem nacionalnog registra genomike i zdravstvenih podataka, što bi bio veliki iskorak ka unapređenju zdravlja građana, a putem primene precizne medicine i preciznog javnog zdravlja.

Izjava o nepostojanju sukobu interesa: Svi autori izjavljuju da ne postoji sukob interesa.
Izjava o finansiranju: Ovu studija je finansirana iz sredstava *MSD Global Oncology Policy Grant*-a; Ministarstva za nauku, tehnološki razvoj i inovacije Republike Srbije, (ugovori br. 451-03-66/2024-03/200110 i br. 451-03-136/2025-03/200043), i iz sredstava *Horizon Europe STEPUPIORS Project* (*HORIZON-WIDERA-2021-ACCESS-03, European Commission, Agreement No. 101079217*). Finansijeri nisu imali nikakvu ulogu u dizajnu studije, prikupljanju i analizi podataka, odluci o objavljivanju ili pripremi rukopisa.

Sukob interesa: Nije prijavljen.

Competing interests: All authors declared no competing interests.
Funding statement: This study was supported by the MSD Global Oncology Policy Grant; the Ministry of Science, Technological Development and Innovation of the Republic of Serbia Agreements No. 451-03-66/2024-03/200110 and No. 451-03-136/2025-03/200043, and the Horizon Europe STEPUPIORS Project (HORIZON-WIDERA-2021-ACCESS-03, European Commission, Agreement No. 101079217). The funders had no role in the study design, data collection and analysis, the decision to publish, or the preparation of the manuscript.

Conflict of interest: None declared.

LITERATURA / *REFERENCES*

1. Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. [Internet]. 2024 [accessed 2025 February 25]. Available from: https://gco.iarc.who.int/media/globocan/factsheets/populations/688-serbia-fact-sheet.pdf
2. International Agency for Research on Cancer. WHO. Global Cancer Observatory: Cancer TODAY. Data version: Globocan 2022 (version 1.1) - 08.02.2024. [Internet]. [accessed 2025 February 25]. Available from: https://gco.iarc.who.int
3. The Tobacco Atlas (a partnership between Vital Strategies and Tobacconomics at Johns Hopkins University). Country Factsheets. Serbia. [Internet]. 2024 [accessed 2025 February 25]. Available from: https://tobaccoatlas.org/factsheets/serbia/
4. WHO Regional Office for Europe. Health impact of ambient air pollution in Serbia: a call to action. WHO. [Internet]. 2019 [accessed 2025 February 25]. Available from: https://serbia.un.org/sites/default/files/2019-10/Health-impact-pollution-Serbia_0.pdf
5. Cavic M, Nikolic N, Marinkovic M, Damjanovic A, Krivokuca A, Tanic M, et al. Two Decades of Progress in Personalized Medicine of Colorectal Cancer in Serbia-Insights from the Institute for Oncology and Radiology of Serbia. Biomedicines. 2024 Oct 8;12(10):2278. doi: 10.3390/biomedicines12102278.
6. Statistical Office of the Republic of Serbia (SORS). Statistical Release, 03.07.2023. [Internet]. 2023 [accessed 2025 February 25]. Available from: https://www.stat.gov.rs/en-us/vesti/statistikalrelease/?p=13622
7. Statistical Office of the Republic of Serbia (SORS). [Internet]. 2025. [accessed 2025 February 27]. Available from: https://data.stat.gov.rs/Home/Result/180706?languageCode=en-US&displayMode=table
8. Uredba o nacionalnom programu ranog otkrivanja karcinoma grlića materice. (Decree on the National Program for Early Detection of Cervical Cancer). Službeni glasnik RS. 73/2013, 83/2013. [Internet]. 2013 [accessed 2025 February 25]. Available from: https://www.pravno-informacioni-sistem.rs/SlGlasnikPortal/eli/rep/sgrs/vlada/uredba/2013/83/2
9. Uredba o nacionalnom programu ranog otkrivanja karcinoma dojke. (Decree on the National Program for Early Detection of Breast Cancer). Službeni glasnik RS. 73/2013-9, 83/2013-3. [Internet]. 2013 [accessed 2025 February 25]. Available from: http://www.pravno-informacioni-sistem.rs/SlGlasnikPortal/eli/rep/sgrs/vlada/uredba/2013/73/1/reg
10. Uredba o nacionalnom programu ranog otkrivanja kolorektalnog karcinoma. (Decree on the National Program for Early Detection of Colorectal Cancer). Službeni glasnik RS. 73/2013-15. [Internet]. 2013 [accessed 2025 February 25]. Available from: https://www.pravno-informacioni-sistem.rs/SlGlasnikPortal/eli/rep/sgrs/vlada/uredba/2013/73/3
11. Institute of Public Health of Serbia (IPHS) "Dr Milan Jovanović Batut". National Cancer Screening Office. [Internet]. 2013. Available from: https://www.skriningsrbija.rs/eng/general-information-about-screening/
12. Bjegovic-Mikanovic V, Vasic M, Vukovic D, Jankovic J, Jovic-Vranes A, Santric-Milicevic M, et al. Serbia: Health system review. Health Systems in Transition, 2019;21(3):i-211.
13. Eurostat. Cancer screening statistics. [Internet]. [accessed 2025 February 27]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Cancer_screening_statistics.
14. Istraživačko-razvojni institut za veštačku inteligenciju Srbije. Primena AI u mamografiji. [Internet]. [accessed 2025 February 27]. Available from: https://ivi.ac.rs/project/primena-ai-u-mamografiji/

15. Silva HECD, Santos GNM, Leite AF, Mesquita CRM, Figueiredo PTS, Stefani CM, et al. The use of artificial intelligence tools in cancer detection compared to the traditional diagnostic imaging methods: An overview of the systematic reviews. PLoS One. 2023 Oct 5;18(10):e0292063. doi: 10.1371/journal.pone.0292063.
16. Rodríguez-Ruiz A, Krupinski E, Mordang JJ, Schilling K, Heywang-Köbrunner SH, Sechopoulos I, et al. Detection of Breast Cancer with Mammography: Effect of an Artificial Intelligence Support System. Radiology. 2019 Feb;290(2):305-314. doi: 10.1148/radiol.2018181371.
17. Bao C, Shen J, Zhang Y, Zhang Y, Wei W, Wang Z, et al. Evaluation of an artificial intelligence support system for breast cancer screening in Chinese people based on mammogram. Cancer Med. 2023 Feb;12(3):3718-3726. doi: 10.1002/cam4.5231.
18. Konstantinidis K. The shortage of radiographers: A global crisis in healthcare. J Med Imaging Radiat Sci. 2024 Dec;55(4):101333. doi: 10.1016/j.jmir.2023.10.001.
19. Eisemann N, Bunk S, Mukama T, Baltus H, Elsner SA, Gomille T, et al. Nationwide real-world implementation of AI for cancer detection in population-based mammography screening. Nat Med. 2025. doi: 10.1038/s41591-024-03408-6. Online ahead of print.
20. Hernström V, Josefsson V, Sartor H, Schmidt D, Larsson AM, Hofvind S, et al. Screening performance and characteristics of breast cancer detected in the Mammography Screening with Artificial Intelligence trial (MASAI): a randomised, controlled, parallel-group, non-inferiority, single-blinded, screening accuracy study. Lancet Digit Health. 2025 Mar;7(3):e175-e183. doi: 10.1016/S2589-7500(24)00267-X.
21. Khoury MJ, Iademarco MF, Riley WT. Precision Public Health for the Era of Precision Medicine. Am J Prev Med. 2016 Mar;50(3):398-401. doi: 10.1016/j.amepre.2015.08.031.
22. Koleva-Kolarova R, Buchanan J, Vellekoop H, Huygens S, Versteegh M, Mölken MR, et al.; HEcoPerMed Consortium. Financing and Reimbursement Models for Personalised Medicine: A Systematic Review to Identify Current Models and Future Options. Appl Health Econ Health Policy. 2022 Jul;20(4):501-524. doi: 10.1007/s40258-021-00714-9.
23. Koleva-Kolarova R, Szilberhorn L, Zelei T, Vellekoop H, Nagy B, Huygens S, et al. Financial incentives to promote personalized medicine in Europe: an overview and guidance for implementation. Per Med. 2023 Jul;20(4):305-319. doi: 10.2217/pme-2022-0145.
24. Genomski ekosistem u Srbiji. Pregled stanja u oblasti. Izveštaj, juni 2023. godine. [Internet] 2023 [accessed 2025 February 27]. Available from: https://c4ir.rs/wp-content/uploads/2024/02/Genomski-ekosistem-SRB-CIR-1.pdf
25. Blic. [Internet] 2024 [accessed 2025 February 27]. Available from: https://zdravlje.blic.rs/aktuelnosti/srbija-vise-nego-ikada-ulaze-u-inovativne-lekove-direktorka-rfzo-otvorila/3d74x2r
26. Kee F, Taylor-Robinson D. Scientific challenges for precision public health. J Epidemiol Community Health. 2020 Apr;74(4):311-314. doi: 10.1136/jech-2019-213311.
27. The Lancet Public Health. Next generation public health: towards precision and fairness. Lancet Public Health. 2019 May;4(5):e209. doi: 10.1016/S2468-2667(19)30064-7.
28. Horton R. Offline: In defence of precision public health. Lancet. 2018 Oct 27;392(10157):1504. doi: 10.1016/S0140-6736(18)32741-7.
29. Roberts MC, Holt KE, Del Fiol G, Baccarelli AA, Allen CG. Precision public health in the era of genomics and big data. Nat Med. 2024 Jul;30(7):1865-1873. doi: 10.1038/s41591-024-03098-0.
30. Williams MS. Population Screening in Health Systems. Annu Rev Genomics Hum Genet. 2022 Aug 31;23:549-567. doi: 10.1146/annurev-genom-111221-115239.
31. Genomics England, official website. 100 000 genomes project. [Internet]. [accessed 2025 February 27]. Available from: https://www.genomicsengland.co.uk/initiatives/100000-genomes-project
32. European Commission. Shaping Europe's digital future. European "1+ Million Genomes" Initiative. [Internet]. [accessed 2025 February 27]. Available from: https://digital-strategy.ec.europa.eu/en/policies/1-million-genomes
33. The Genome of Europe initiative. [Internet]. [accessed 2025 February 27]. Available from: https://b1mg-project.eu/1mg/genome-europe
34. Drljaca T, Zukic B, Kovacevic V, Gemovic B, Klaassen-Ljubicic K, Perovic V, et al. The first insight into the genetic structure of the population of modern Serbia. Sci Rep. 2021 Jul 7;11(1):13995. doi: 10.1038/s41598-021-93129-4.
35. Centar za četvrtu industrijsku revoluciju u Srbiji. Centar deo konzorcijuma Genome Europe, vest 23.11.2023. [Internet]. [accessed 2025 February 27]. Available from: https://c4ir.rs/centar-deo-konzorcijuma-genome-of-europe/
36. Ministartsvo prosvete Republike Srbije. Javni poziv MASTER 4.0 za izbor studijskih programa master akademskih studija iz oblasti bioinformatike. (Ministry of Education of the Republic of Serbia). [Internet]. [accessed 2025 February 27]. Available from: https://prosveta.gov.rs/vesti/javni-poziv-master-4-0-za-izbor-studijskih-programa-master-akademskih-studija-iz-oblasti-bioinformatike/
37. Centar za četvrtu industrijsku revoluciju u Srbiji. Projekat DNK skrininga. Iskoristi svoje genetičke informacije za zdraviju budućnost. [Internet]. [accessed 2025 February 27]. Available from: https://c4ir.rs/sr-rs/projekat-02-cir/
38. Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GL; Guideline Development Group, American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and National Society of Genetic Counselors Practice Guidelines Committee. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med. 2015 Jan;17(1):70-87. doi: 10.1038/gim.2014.147.
39. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007 Apr 10;25(11):1329-33. doi: 10.1200/JCO.2006.09.1066.
40. Armstrong N, Ryder S, Forbes C, Ross J, Quek RG. A systematic review of the international prevalence of BRCA mutation in breast cancer. Clin Epidemiol. 2019 Jul 11;11:543-561. doi: 10.2147/CLEP.S206949.
41. Mucci LA, Hjelmborg JB, Harris JR, Czene K, Havelick DJ, Scheike T, et al; Nordic Twin Study of Cancer (NorTwinCan) Collaboration. Familial Risk and Heritability of Cancer Among Twins in Nordic Countries. JAMA. 2016 Jan 5;315(1):68-76. doi: 10.1001/jama.2015.17703.
42. Krivokuca A, Boljevic I, Jovandic S, Magic Z, Mandic A, Tomasevic Z, et al. Germline mutations in cancer susceptibility genes in high grade serous ovarian cancer in Serbia. J Hum Genet. 2019 Apr;64(4):281-290. doi: 10.1038/s10038-019-0562-z.
43. Nelson HD, Pappas M, Cantor A, Haney E, Holmes R, Stillman L. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA1/2-Related Cancer in Women: A Systematic Review for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2019 Aug. Report No.: 19-05251-EF-1.
44. Murray MF, Evans JP, Khoury MJ. DNA-Based Population Screening: Potential Suitability and Important Knowledge Gaps. JAMA. 2020 Jan 28;323(4):307-308. doi: 10.1001/jama.2019.18640.
45. Robertson AJ, Mallett AJ, Stark Z, Sullivan C. It Is in Our DNA: Bringing Electronic Health Records and Genomic Data Together for Precision Medicine. JMIR Bioinform Biotechnol. 2024 Jun 13;5:e55632. doi: 10.2196/55632.
46. World Cancer Research Fund. Lung Cancer Statistics. [Internet]. 2022 [accessed 2025 February 27]. Available from: https://www.wcrf.org/preventing-cancer/cancer-statistics/lung-cancer-statistics/?utm_source=chatgpt.com

47. Buchanan AH, Lester Kirchner H, Schwartz MLB, Kelly MA, Schmidlen T, Jones LK, et al. Clinical outcomes of a genomic screening program for actionable genetic conditions. Genet Med. 2020 Nov;22(11):1874-1882. doi: 10.1038/s41436-020-0876-4.
48. Hayward J, Evans W, Miller E, Rafi I. Embedding genomics across the NHS: a primary care perspective. Future Healthc J. 2023 Nov;10(3):263-269. doi: 10.7861/fhj.2023-0116.
49. Wildin RS, Giummo CA, Reiter AW, Peterson TC, Leonard DGB. Primary Care Implementation of Genomic Population Health Screening Using a Large Gene Sequencing Panel. Front Genet. 2022 Apr 25;13:867334. doi: 10.3389/fgene.2022.867334.
50. Wilson JMG, Jungner G. Principles and practice of screening for disease. Geneva: World Health Organization. 1968.
51. Turnbull C, Firth HV, Wilkie AOM, Newman W, Raymond FL, Tomlinson I, et al. Population screening requires robust evidence-genomics is no exception. Lancet. 2024 Feb 10;403(10426):583-586. doi: 10.1016/S0140-6736(23)02295-X.
52. Guzauskas GF, Garbett S, Zhou Z, Schildcrout JS, Graves JA, Williams MS, et al. Population Genomic Screening for Three Common Hereditary Conditions: A Cost-Effectiveness Analysis. Ann Intern Med. 2023 May;176(5):585-595. doi: 10.7326/M22-0846.
53. Guzauskas GF, Garbett S, Zhou Z, Spencer SJ, Smith HS, Hao J, et al. Cost-effectiveness of Population-Wide Genomic Screening for Hereditary Breast and Ovarian Cancer in the United States. JAMA Netw Open. 2020 Oct 1;3(10):e2022874. doi: 10.1001/jamanetworkopen.2020.22874.
54. Wei X, Sun L, Slade E, Fierheller CT, Oxley S, Kalra A, et al. Cost-Effectiveness of Gene-Specific Prevention Strategies for Ovarian and Breast Cancer. JAMA Netw Open. 2024 Feb 5;7(2):e2355324. doi: 10.1001/jamanetworkopen.2023.55324.
55. Mansur A, Zhang F, Lu CY. Association between Health Insurance Type and Genetic Testing and/or Counseling for Breast and Ovarian Cancer. J Pers Med. 2022 Jul 31;12(8):1263. doi: 10.3390/jpm12081263.
56. Roberts MC, Allen CG. Next-Generation Public Health Genomics: A Call to Assess the Equitable Implementation, Population Health Impact, and Sustainability of Precision Public Health Applications. Public Health Genomics. 2024;27(1):30-34. doi: 10.1159/000535579.
57. Ollis S, Kovačević M, Djikanovic B, Radoman N, Smigic I, Barry MA. Maturity Assessment of the Health Information System Using Stages of Continuous Improvement Methodology: Results From Serbia. Glob Health Sci Pract. 2024 Oct 29;12(5):e2400083. doi: 10.9745/GHSP-D-24-00083.
58. Centre for the Fourth Industrial Revolution Network. Network Impact Report 2022/2023. Centre for the Fourth Industrial Revolution, World Economic Forum. [Internet]. 2024 [accessed 2025 January 27]. Available from: https://c4ir.rs/wp-content/uploads/2024/01/WEF_C4IR_Network_Impact_Report_2022-2023.pdf
59. Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data. 2016 Mar 15;3:160018. doi: 10.1038/sdata.2016.18.