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in Medicine

# State of innovation

2019

# **State of Innovation** 2019 - Summary

IMMUNO-ONCOLOGY: The Nobel Prize for checkpoint inhibitors

CAR-T CELL THERAPY: first approvals in the European Union

PERSONALIZED MEDICINE: biomarkers and precision diagnosis of cancer

GENOMIC MEDICINE: challenges in the implementation in the health system

HEMOPHILIA, GOAL OF "ZERO BLEEDING": personalization of treatment, mobile apps, extended half-life products, monoclonal antibodies, gene therapies

BIOTECHNOLOGY AND BIOLOGICAL MEDICINES: added value for the health system

DIABETES: major paradigm shift

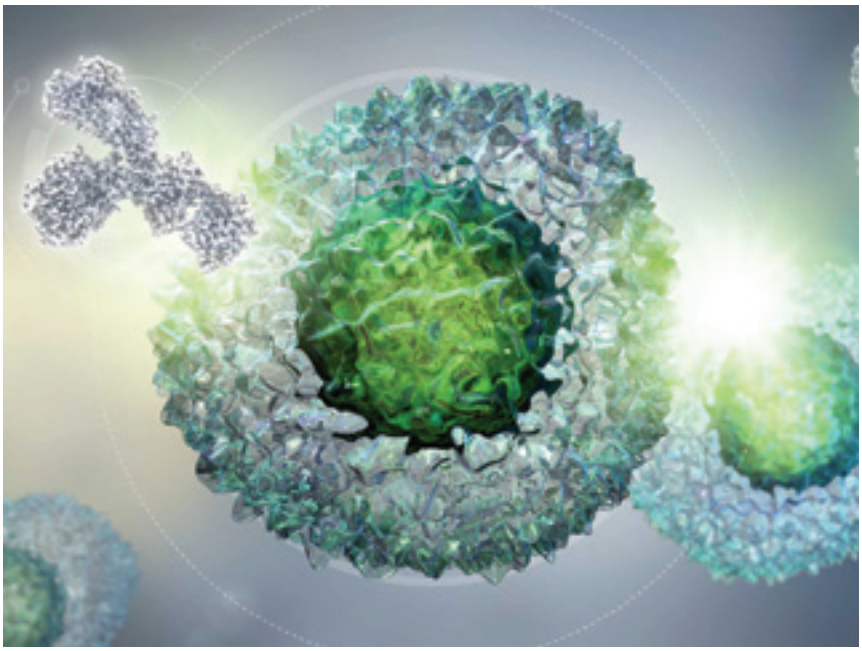
ELIMINATION OF HEPATITIS C: from medical stage to societal approach

DIGITAL MEDICINE: development of a national strategy in the European context

Innovative medicines approved by EMA in the period from 1st January 2018 to 30th April 2019

# IMMUNO-ONCOLOGY: The Nobel Prize for checkpoint inhibitors

## Concept



Immuno-oncology is a relatively new field in cancer management, although the concern to understand the mechanisms through which the immune system could fight against cancer is over 100 years old. Hundreds of cancer cells are produced in one day in the human body, but not all people get to develop a form of cancer because the immune system manages to eliminate them, recognizing them as "non-self". The occurrence of cancer is also accompanied by the "paralysis" of the immune system, which fails to fight effectively against malignant cells. The development of medicines to "awaken" the immune system is an old concern of the medical world, but the first immuno-oncological drug was approved only in 2010. Unlike chemotherapy (which attacks both cancer cells and normal body cells, resulting in severe side effects) and targeted anti-cancer treatments (which act by selecting only cancer cells), immuno-oncological medicines act only in the connections of the immune system, which they reactivate in the fight against cancer. There are several categories of immuno-oncological medicines in the process of development or already on the market, including: checkpoint inhibitors, CAR-T cell therapies and vaccines.

## The present moment

In October 2018, Tasuku Honjo and James Allison received the Nobel Prize for Medicine for their work on the development of the checkpoint inhibitors, thus the field of immune-oncology enjoying the highest recognition of a scientific forum. Two months later, in December 2018, the Centre for Innovation in Medicine launched the "White Paper of Immuno-Oncology", a public policy document which aims to contribute to ensuring the access to these therapies for patients in

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Romania.

According to the recently published data under the aegis of the European Society for Medical Oncology[1], worldwide there are 2,004 immunotherapies in the process of development or are already entered on the market, addressing a number of 303 types of cancer. 3,042 studies evaluate these therapies, which are developed by 864 companies. 17 types of cancer already have at least one immunotherapy as an approved treatment option.

In the past 3 years, 5 checkpoint inhibitors (and there are still 1,502 ongoing clinical trials with these molecules), 2 CAR-T cell therapies (other such 162 therapies are in clinical trial phase) and a bispecific antibody anti-CD3 have received marketing authorization in the European Union. There are 244 ongoing clinical trials with various types of cell therapies, not only CAR-T, for cancer therapy.

1,105 clinical trial assess potential combinations between the check-point inhibitors (nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab) and other types of cancer therapies (chemotherapy, targeted therapies, angiogenesis inhibitor therapy, radiotherapy, other types of immunotherapy) – only in 2017, 469 new such clinical trials were initiated.

Since 2011, the European Medicines Agency has approved immuno-oncology medicines for several cancer localizations as follows:

- Malignant melanoma (4 molecules)
- Non-small cell lung cancer (3 molecules)
- Classical Hodgkin's lymphoma (2 molecules)
- Urothelial carcinoma (2 molecules)
- Renal cell cancer (1 molecule)
- Head and neck cancer (2 molecules)
- Merkel cell carcinoma (1 molecule)

**1.105**

**clinical trials assess** potential combinations between checkpoint inhibitors (nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab) and the other types of cancer therapies (chemotherapy, targeted therapies, angiogenesis inhibitor therapies, radiotherapy, other types of immunotherapy)

1 https://academic.oup.com/annonc/article/29/1/84/4693829





The access of the oncological patients to immuno-oncological medicines in Romania is achieved by means of cost and volume contracts, contracts for non-small cellular lung cancer, malignant melanoma, renal cell cancer and Hodgkin's lymphoma are currently under way.

## Recommendations for action (According to the White Paper of Immuno-Oncology)

**1. Ensuring a strategic framework for cancer control**

1.1. Cancer prioritization by the Government in the context of the increase of the disease burden at national level

1.2. Development of the National Cancer Plan and the National Cancer Registry

1.3. Development of a precision diagnosis programme for cancer. In those types of cancer in which biomarkers are validated scientifically and for those medicines whose prescription is conditioned by the existence of a biomarker, the patient should not receive any treatment prior to the mandatory testing of biomarkers. Making a precision diagnosis determines the choice of a personalized drug, depending on the molecular profile, avoiding unnecessary costs (direct - with the treatment given to patients who would not benefit anyway, and indirectly - associated with the side effects of the administered medicines in the absence of a specific test)

1.4. Development of primary prevention programmes at national level aimed at smoking, obesity and alcohol consumption and secondary prevention programmes for cervical, colorectal and breast cancer;

1.5. Establishment of the National Cancer Registry and development of other essential ICT instruments, and the electronic file of the patient, very useful especially for oncological pathology in the context of massive accumulation of medical data. Creation and development of these ICT components might also create the premises for restarting the clinical research in oncology in Romania (on the basis of bioinformatics)

**2. Ensuring the necessary framework for the implementation of the strategic plan and its monitoring**

2.1. Consolidating and expanding the comprehensive cancer centers with multidisciplinary approach

2.2. Connecting local oncology centers to a regional/national network of tumor boards

**3. Accelerating the time required for ensuring the access of the patients to new therapies**

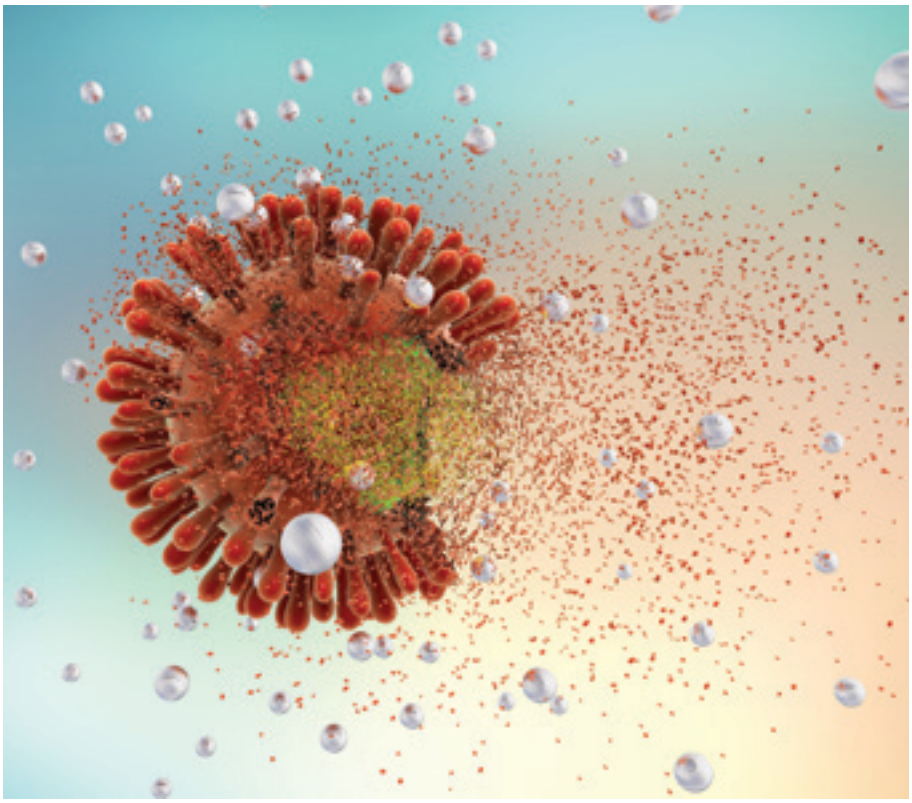
3.1. Introducing the long-term pharma-economic assessment for new therapies, including the introduction of a rapid method of assessment and compensation for immuno-oncological medicines that prove their value quickly in clinical trials and are recognized as such by EMA
3.2. Definition of the legislation in matters of compassionate use and other early access mechanisms, which might favor inclusive access to immunotherapy
3.3. Improving the reimbursement methodology in order to allow the conclusion of multi-annual cost and volume contracts.

**4. Improving the sustainability of cancer control**

4.1. Increasing the national oncology budgets, taking into account the higher mortality rates and the unfavorable mortality/incidence ratio
4.2. Establishing a fund for access to innovation to cover the costs of new cancer immune-therapies, in the first phases of use, but also to guarantee ongoing access to these therapies
4.3. Addressing the ineffective consumption of resources and redirecting the resources to financing of interventions that provided to be effective, such as immuno-oncology drugs
4.4. Developing the infrastructure for clinical trials in order to facilitate early access of patients, including to immuno-oncology drugs

# CAR-T CELL THERAPIES: first approvals in the European Union

## Concept



Unlike conventional therapies in oncology (chemotherapy, radiotherapy or surgery), immunotherapy is a new method that uses the ability of the immune system to identify and destroy tumor cells. CAR-T is a special type of immunotherapy that imposes a new standard in personalizing cancer treatment.

ASCO experts (American Society of Clinical Oncology) define it as "gene therapy, cell therapy and immunotherapy".

The development of the CAR-T therapies involves a unique manufacturing circuit. If the conventional medicines are mass-produced and get from the laboratory to the patient, for CAR-T therapies, there is a particular mechanism that begins from the patient. Each treatment is created for one individual. The patient's immune cells are sampled and modified in special labs and reintroduced in the body.

T cells are genetically reprogrammed to express chimeric receptors on their surface. These immunoreceptors were called „chimeras" because they are formed of different components – fragments of synthetic antibodies called domains. They recognize specific structures called antigens on the surface of the tumor cells. The antigens in each cancer cells are different from one type of neoplasm to another and each CAR is made for a particular antigen.

CAR-T cell therapies against CD19 antibody proved unprecedented results in patients with hematological cancers such as acute lymphoblastic leukemia (ALL) and subtypes of non-Hodgkin's lymphoma. Studies report a complete remission rate between 70 and 94%

For instance, in certain types of leukemia or lymphoma in the malignant cells, there is an antibody called CD-19. CAR-T therapies created for these types of neoplasia will work only if cancer cell express CD-19[1]. CD-19 is the most frequent target for CAR-T at present, and 56 therapies targeted against this antigen are included in clinical trials.

CD19-targeted CAR-T cell therapies have shown unprecedented results in patients with hematological cancers such as acute lymphoblastic leukemia (ALL) and subtypes of non-Hodgkin's lymphoma. Studies report complete remission rates between 70 and 94%[2]. These results are encouraging especially because they have been obtained in patients with refractory forms of illness for which all therapeutic options were exhausted.

## The present moment

The first two CAR-T cell therapies that received FDA approval in 2017 were Kymriah (tisagenlecleucel), with indication in ALL, and Yescarta (axicabtagen ciloleucel) for diffuse large B-cell lymphoma (DLBCL), the most common form of non-Hodgkin's lymphoma. In May 2018, the FDA extends approval for Kymriah also in patients with refractory or relapsed DLBCL[3]. Thus, Kymriah becomes the first CAR-T therapy with two indications in hematological neoplasms. The American Society of Clinical Oncology (ASCO) has designated CAR-T cell therapies as Innovation of the Year 2018.

One year after the approval in the USA, the CAR-T therapies, Kymriah and Yescarta, were also approved in the European Union, each of them with two indications.

Kymriah is indicated in children and young people under 25 years of age with refractory or recurrent form of ALL and in adults with DLBCL. Yescarta received approval for DLBCL and for primary mediastinal large B-cell lymphoma.

The patients in UK had quick access to such therapies through a historic decision issued in October 2018 by the NHS - National Health Services.

The development of CAR-T therapies involves a unique manufacturing circuit. If the conventional medicines are mass-produced and get from the lab to the patient, for CAR-T therapies, there is a particular mechanism that begins from the patient. Each treatment is created for one individual. The patient's immune cells are sampled and modified in special labs and reintroduced in the body.

1 https://raportuldegarda.ro/articol/procesul-obtinere-car-t-extragerea-celulelor-imune-organism/
2 https://jhoonline.biomedcentral.com/articles/10.1186/s13045-017-0423-1
3 https://www.novartis.com/news/media-releases/kymriahr-tisagenlecleucel-first-class-car-t-therapy-from-novartis-receives-second-fda-approval-treat-appropriate-rr-patients-large-b-cell-lymphoma



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2019 "STATE OF INNOVATION" REPORT

Under the Cancer Drugs Fund programme, it was decided to subsidize the CAR-T therapy for patients up to 25 years of age, with acute B-cell refractory and recurrent lymphoblastic leukemia.

Simon Stevens, the NHS President, described the importance of this moment as: „One of the quickest funding approvals in the history of NHS spanning 70 years".

The costs of CAR-T therapies amount to hundreds of thousands of dollars, and therefore, a great challenge is to identify feasible funding methods for these therapies. The US National Health Insurance System, Centers for Medicare and Medicaid Services (CMS), introduced, in 2001, a payment system for innovative technologies that require high costs - New-Technology Add-On Payments[4]. This funding method means adding 50% of the costs of the new technologies to the amount allocated under DRG. According to the new 2019 regulations, CMS proposed the increase of this additional budget for the CAR-T therapies from 50% to 60% for 2020.

A report by the Cancer Research Institute on cellular therapies was published in May 2018. Since September 2017, the production of new cellular therapies for oncology has begun, which means an increase of 87% in less than 7 months. 7 classes of cell therapies and 113 targets have been identified for these. At present, 753 cell therapies for oncology are under development and 375 clinical trials assess these therapies[5]. Clinical trials show impressive remission rates, even of over 90% for several types of cancers[6]. Most CAR-T studies recruit patients who did not respond to other available treatment.

A study presented at the Annual Meeting of the American Society of Hematology 2018 (ASH) shows how important it is to prepare the medical community to understand the new therapies that are approved quickly: 61% of the assessed clinicians (hematologists or oncologists) failed to identify the components of a CAR receptor, while 45% did not know that the approved CAR-T therapies are administered through a single infusion. Moreover, 62% did not know the indications for which Yescarta[7] was approved.

Under the Cancer Drugs Fund programme, it was decided to subsidize the CAR-T therapy for patients of up to 25 years of age, with acute refractory or recurrent cell-B lymphoblastic leukemia.
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4 https://s3.amazonaws.com/public-inspection.federalregister.gov/2019-08330.pdf
5 https://www.cancerresearch.org/news/2018/global-landscape-of-cancer-cell-therapy-report
6 https://jhoonline.biomedcentral.com/articles/10.1186/s13045-017-0423-1
7 https://www.healio.com/hematology-oncology/lymphoma/news/print/hemonc-today/%7B0b94ed2c-a688-4f73-96bd-100c731d0f63%7D/new-indications-may-accelerate-explosion-in-car-t-cell-therapy-but-more-education-still-needed?page=5

A great challenge in CAR-T therapies is to extend the use in solid tumors. At the beginning of 2019, a study conducted at Memorial Sloan Kettering Cancer Center (MSKCC) proved the first positive results for CAR-T therapies in the case of HER2-positive sarcomas and malignant mesothelioma: the combination between the CAR-T therapy and the checkpoint inhibitors provide response rate of over 70% in patients with these types of neoplasms[8]. At present, over 30 antigens associated with solid tumors are evaluated in studies aimed at CAR-T cell therapies.

**7 classes of cell therapies** and **113 targets** were identified for them. At present, **753 cell therapies** for oncology are under development, and **375 clinical trials** evaluate these therapies.

## Recommendations

- The approval in EU of the first CAR-T cell therapies causes the Romanian health system to face unprecedented challenges, because ensuring the access of patients to these therapies requires multilevel transformations: modern infrastructure, professional training, HTA assessment and coverage by the public health insurance system. In this respect, we recommend the setting up of a working group within a PPP to develop a strategy and an action plan for CAR-T in Romania.

8 https://raportuldegarda.ro/articol/terapiile-car-t-eficiente-cazul-tumorilor-solide-primele-rezultate-pozitive-studii-faza-i/

# PERSONALIZED MEDICINE: biomarkers and cancer precision diagnosis

## Concept

The concept of personalized (precision) medicine was brought into the public agenda, on a global scale, in January 2015 by former US President Barack Obama. In the State of the Union Address, Barack Obama launched the Initiative for Precision Medicine[1], whose goal is "the development of the means of disease prevention and treatment, which takes into account people's individual variations in genes, living environment and lifestyle".

The concept of personalized medicine is based on the developments in the field of genome sequencing, biomedical technologies, and the ability to analyze and store medical data.

In Europe, the Council of the European Union[2], on the 7th December 2015, granted pan-community policy recognition for "personalized medicine for patients", placing the theme among the EU priorities in the next decade and inviting the Member States and the European Commission to engage in reaching its full potential.

Among the therapeutic areas, oncology benefits the most from this approach. The so-called biomarkers like at the root of precision oncology and of diagnosis accuracy of cancer. A biomarker is a biological feature, which may be molecular, anatomical, physiological or biochemical. These characteristics can be measured and evaluated objectively, becoming indicators of a normal biological or pathological process. Biomarkers can be of several types, depending on their usefulness:

1 https://syndication.nih.gov/multimedia/pmi/infographics/pmi-infographic.pdf
2 http://data.consilium.europa.eu/doc/document/ST-15054-2015-INIT/en/pdf

• Diagnosis biomarkers - show the presence of a disease in the body
• Risk biomarkers - indicate the risk of suffering from a certain disease
• Prognostic biomarkers - give clues to the favorable or aggressive progression of a disease
• Prediction biomarkers - indicate the response and toxicity to a particular treatment

Biomarkers associated with various types of cancers can be identified by specific tests, on the basis of which the oncologist has to establish the individualized dosage regimen for each patient.

## The present moment

In 2018, over 30% of the newly approved drugs in USA were personalized medicines, on the rise as compared to the previous years, and half of them were dedicated to the treatment of cancer[3]. A personalized drug is the drug in which the SPC (summary of product characteristics) refers to various biomarkers, which can be highlighted by diagnostic tests for the purpose of guiding the therapeutic decision for a certain patient.

Non-small cell lung cancer benefits to the fullest extent from the in-depth understanding of biology by highlighting biomarkers. In November 2018, the Centre for Innovation in Medicine published the Position Paper “Biomarkers in Non-Small Cell Lung Cancer” to help deliver the first biomarker testing plan for cancer patients in Romania. The principle of the document is “Test! Then treat!”. The paper is recommended by the relevant professional societies (National Society for Medical Oncology in Romania, Romanian Society of Pneumology), the representative associations of patients (Alliance of Chronic Patients in Romania, Coalition of the Organizations of Patients with Chronic Diseases in Romania) and all pharmaceutical companies interested in the field of lung cancer. In addition to lung cancer, breast cancer and melanoma also benefited from the development of biomarkers. Targeted therapies have brought radical changes in the treatment of patients with metastatic melanoma, but also in the adjuvant treatment.

But the molecular mechanisms involved in in carcinogenesis are much more complex than thought, so finding new biomarkers is essential in identifying specific groups of patients who benefit from a particular therapy and preventing the build-up of resistance.

3 http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PM-at-FDA.pdf



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2019 “STATE OF INNOVATION” REPORT

Over 50% of melanomas have the mutation in the BRAF gene, which normally encodes a protein kinase which plays a role in cell differentiation, proliferation and survival. At present, BRAF is the only validated biomarker, predictive for the response to treatment, but many other biomarkers are in the course of evaluation. The BRAF inhibitors determine higher response rates in patients with melanoma, but the responses are short-lived. The studies show that patients identified with BRAF V600E mutation also have other molecular abnormalities that influence the response to treatment. Simultaneous abnormalities cause the reactivation of the signalling pathways dependent on MAP kinase. Thus, it was observed that by inhibiting another enzyme (MEK) involved in this signalling pathway, better responses are obtained[4]. For instance, if in the case of monotherapy with BRAF inhibitors, the studies report a general response rate of approximately 50%, the therapy combined with a MEK inhibitor increases the response rate of up to 70%. Being a tumor type with a great heterogeneity, other mechanisms are influenced in melanoma, such as those by which the cancer cells escape the detection of the immune system. PD-1 and CTLA-4, two molecules on the surface of T lymphocytes are other important markers and represent the targets of immunotherapy approved by FDA and EMA for melanoma. However, the combination between targeted therapies and immunotherapy is a new challenge, as there are over 1,000 clinical trials evaluating different combinations in which immunotherapy is included. In order to overcome resistance, the studies indicate the need for integrative approaches that include the interfering of multiple signalling pathways. The establishing of biomarkers to guide these strategies will be essential in the control of melanoma.

In 2018, 15% of the mortality in female population was determined by breast cancer. In the past 20 years, hormonal therapies for metastatic breast cancer HR+ (hormone receptor +) have remained unchanged. Although the estrogen receptor is an important target in the treatment of the disease, half of the patients develop resistance. The new therapeutic targets are molecules involved in different signalling pathways which allow the activation of the ER receptor independently from the hormone stimulus. Targeted therapies have been developed to inhibit these signalling pathways.

Approximately 40% of the ER+(estrogen receptor) breasts cancers, HER2 - exhibit mutations activating PIK3CA (phosphatidylinositol 3-kinase) that

4 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3079374/

favor the resistance to hormone therapy and the disease progression[5]. This mutation is also found in 20% of HER2 + cancers, a more aggressive form of the disease and is associated with resistance to chemotherapy and anti-HER2 treatments. The PIK3CA gene encodes a family of proteins involved in different types of cellular processes, angiogenesis and apoptosis. The PIK3CA mutation is considered an independent negative prognostic factor, according to a recent meta-analysis[6]. The response of these patients to tyrosine kinase inhibitors such as lapatinib and trastuzumab is much lower. The PI3K mutation is also predictive of the response to adjuvant hormone therapy[7]. The signalling pathway of which these proteins are part, PI3K/AKT/mTOR, is complex and the strategies of therapeutic intervention are faced with numerous challenges. Up to 8% of breast cancers exhibit the AKT1 mutation, which occurs especially in tumors exhibiting both estrogen and progesterone receptors. The AKT activation determines an unfavorable prognosis in patients with breast cancer that receive endocrine therapy. Another mutation which may occur during hormone therapy is mTOR. Adding everolimus targeted therapy to the endocrine treatment has proved favorable effects on the development of resistance.

The cyclin-dependent CD4 and CDK6 inhibitors have proved effective both in pre-menopausal and post-menopausal women with HR+, HER2 - breast cancer. Ribociclib, one of the representatives of this class was approved in 2017 by FDA and EMA and proved, in several 3-phase 1st line clinical trials, sustained benefits along with hormonal therapy[8]. All mechanisms involved in resistance to treatment of patients with breast cancer suggest the importance of a multi-target strategy, and the identification of the proper strategy for each patient depends on establishing the biomarkers.

Another important aspect related to the modern management of cancer is multidisciplinary teams (tumor board). A multidisciplinary team consist of, in addition to the oncologist and the anatomopathological physician, the medical imaging specialist, radiation therapist and surgeon. The study data show that the patient management within the multidisciplinary team increases the survival rate[9].

## Recommendations for action

5 https://www.onclive.com/publications/oncology-live/2018/vol-19-no-14/pik3ca-remains-elusive-in-breast-cancer
6 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5995110/
7 https://jamanetwork.com/journals/jamaoncology/article-abstract/2684628
8 https://www.ema.europa.eu/en/medicines/human/EPAR/kisqali
9 Stone E. et al. Lung Cancer 2018; 124-199-204



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2019 “STATE OF INNOVATION” REPORT

- Development of a precision diagnostic programme for cancer. In those types of cancer in which biomarkers are validated scientifically and for those medicines whose prescription is conditioned by the existence of a biomarker, the patient should not receive any treatment before the mandatory performance of the tests of biomarkers.
- The establishment, at the level of the national health insurance fund (CNAS), of a fund to cover the cost of the tests required for precision diagnosis of cancer, to which the private sector should also contribute proportionally.
- For non-small cell lung cancer specifically, to follow the recommendation in the Position Paper “Biomarkers in non-small cell lung cancer”, developed by the Centre for Innovation in Medicine.
- Establishment of the National Cancer Registry and development of other essential digital tools, such as the patient’s electronic file, very useful for oncological pathology in the context of massive accumulation of medical data.
- Under the cancer precision diagnosis programme, the development of a national network of laboratories for the cancer precision diagnosis, equipped at the highest professional and technological standards (NGS).
- Defining a quick method of evaluation and public health insurance coverage for personalized medicines and specific tests which quickly prove their value in clinical trials.
- Inclusion of personalized medicine among the quality criteria in the accreditation of hospitals and oncological centers, in particular.

# GENOMIC MEDICINE: challenges in the implementation in the health system

## Concept

Genomic medicine is an emerging medical field, which involves the use of a person's genomic information as part of the healthcare needed and provided in the health system, (e.g. for diagnosis and therapeutic decision), in the context of the evaluation of the therapeutic results thus obtained, to ensure access for all those who might benefit from this new approach.[1] The field of genomic medicine has derived from the extensive research project on the human genome, which led to its decoding at the beginning of the 21st century.

The identification of the sequence of approximately 3 billion of base pairs in the human genome opened a new stage in modern medicine. The causes of many diseases were elucidated by the new exome sequencing techniques (those regions in the genome encoding proteins). These represent only 2% of the genome, but include 85% of the genetic variants associated with human pathology. Likewise, genomic medicine allowed for the identification of the best therapeutic strategies for certain types of cancers, allowed for the diagnosis of rare diseases or preventive interventions. The applications of genomic medicine currently influence all essential aspects in addressing a patient, from determining the risk of developing a disease and the establishing of the diagnosis to treatment[2]. Genomic medicine is considered a form of personalized medicine.

100 FDA-approved medicines contain in the SPC (summary for product characteristics) data on pharmacogenomics that is the ability of a patient to respond favorably to a gene-based treatment.

Gene therapies most often define treatment methods that involve the replacement of an abnormal or absent gene. A vector delivers a functional gene in the nucleus, and the cell will produce the necessary protein. These

1 https://www.genome.gov/27527652/genomic-medicine-and-health-care/
2 https://ghr.nlm.nih.gov/primer/therapy/genetherapy



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2019 "STATE OF INNOVATION" REPORT

are also called gene replacement therapies. Many such therapies are evaluated in clinical trials and, in the past years, a few have received approval from the authorities. However, the spectrum of therapeutic interventions on the genome is much broader. Unlike gene replacement therapy which allows for only one type of intervention, the gene editing techniques like CRISPR-Cas allow for direct precision molecular changes that can correct genes[3]. Likewise, CAR-T therapies are a particular form of ex vivo gene therapy which requires the sampling of the patient's T lymphocytes and their reprogramming for cancer cell recognition.

## The present moment

Genomic medicine is already applied in practice, as long as over 100 FDA-approved medicines contain in the SPC (summary of product characteristics) data on pharmacogenomics, that is the ability of a patient to respond favorably to a gene-based treatment based on the genomic information[4]. Infectious diseases, rare diseases, cystic fibrosis and many forms of cancer benefit from this type of information.

**300**
cell and gene therapies are developing in 2019, targeting over 100 diseases. 20 such therapies will be approved every year until 2025, according to new FDA forecasts.

In addition to personalizing the therapy based on genomic data, the development of the gene editing techniques allowed for the publication, at the end of 2017[5], of the first consistent data supporting the use of gene therapy for a series of monogenic diseases, such as Leber's congenital amaurosis, epidermolysis bullosa, spinal muscular atrophy type 1, but also hemophilia A and B.

Luxturna, the treatment for Leber's congenital amaurosis, became, in December 2017, the first direct gene therapy ever approved in the USA[6]. One year later, it also received approval from the European Medicines Agency (EMA), being the first therapy for a hereditary disease approved in the EU. 60% of those suffering from this type of retinal dystrophy, caused by the RPE65 mutation, have a severe form of disease that causes a dramatic deterioration in vision shortly after birth. The loss of vision is progressive and in the absence of treatment, blindness is complete in time. Luxturna is administered only once to the retina, transferring a healthy version of the gene responsible for this disease (RPE65) through a viral vector.

The first gene therapy with beta-thalassemia received the recommendation

3 https://ghr.nlm.nih.gov/primer/genomicresearch/genomeediting
4 https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm
5 https://raportuldegarda.ro/articol/istoric-5-terapii-genice-rezultate-incurajatoare-publicate-in-ultimele-2-luni/
6 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm589467.htm

for approval in the European Union at the end of March. This new therapy (Zynteglo) is administered only once in a lifetime and involves the introduction of functional copies of the beta globin gene in the hematopoietic stem cells harvested from the patient. Zynteglo is for patients with severe forms of beta-thalassemia, which require the long-term dependence of blood transfusion.

On 2nd November 2017, a study was published in the New England Journal of Medicine showing that a single intravenous injection with a new high dose gene therapy extends the survival of patients with type 1 muscular atrophy. The gene therapy for spinal muscular atrophy (Zolgensma) is waiting for the approval decision in the USA. This is an example illustrating the pace at which gene therapies end up at the regulatory authorities nowadays.

The encouraging data from a single phase I study were sufficient for the therapy to receive a priority status from the FDA at the end of 2018. By comparison, 20 years were needed for the approval of the first gene therapy, Glybera, in the European Union,

Regarding hemophilia, a disease that still leads to the death of young people in Romania against the improper control of bleeding, the healing of the disease is already being discussed as a result of the use of gene therapy.

At the same time, extensive mapping projects of the genome of the entire population (Iceland)[7] or only of a segment of the population (UK) were carried out[8], while China announced the largest genomic medicine programme in the world[9]. In Europe, it is expected to launch the Million Europe Genome Analysis (MEGA) project which aims to achieve a cohort of at least one million of EU citizens whose genome is sequenced by the end of 2022[10].

The field of genetic testing directly addressed to the consumer is also in dynamic after FDA approved the marketing directly to the end consumer of a genetic test which, among others, is able to indicate the risk for certain neurologic diseases such as Parkinson disease[11]. At the same time, it is very difficult to anticipate the evolution of this field, after in January 2016, the

> For new technologies to be able to become a reality, it is necessary to re-assess the entire health system. Steven Pearson, President of the Institute for Clinical and Economic Review, USA: „We need to create a system that will not lead us to stop a high-speed train through a wall”.

7 http://content.time.com/time/magazine/article/0,9171,1158968,00.html
8 https://www.genomicsengland.co.uk/
9 https://www.weforum.org/agenda/2017/11/3-ways-china-is-leading-the-way-in-precision-medicine/
10 https://www.karger.com/Article/FullText/481300
11 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm551185.htm



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2019 “STATE OF INNOVATION” REPORT

scientific world took note of the creation of the 6-nucleotide DNA, by the insertion of two synthetic bases (XY) along with the 4 known (ATCG)[12], and the appearance of the first semi-synthetic form of life in history, a species of E.Coli.

In this context, the concern to ensure confidentiality and data protection, the definition of the ownership of such data and the type of consent required for the use of such data become essential.

300 cell and gene therapies are developing in 2019, targeting over 100 diseases. 20 such therapies will be approved every year until 2025, according to the new FDA forecasts. The question: „what is the price of a treatment given only once that can lead to the healing of debilitating diseases?” becomes very important.

Several payment methods have been proposed. A method suggested by the company producing the gene therapy for beta-thalassemia is that of distributing costs over a period of 5 years in a system similar to instalments[13]. Each annual payment will be adjusted depending on the effectiveness of the therapy. If the therapy does not work, the patients have the option to stop the treatment. The blood transfusions needed by the patients with beta-thalassemia are expensive. It was estimated that Zynteglo gene therapy makes savings of approximately 2 million dollars.

Certain gene therapies have indications in diseases that are prevalent in poorly developed countries, such as sickle cell disease (SCD). There have always been discrepancies between the access to treatment between nations. However, gene therapies are an option with curative potential, which is different from everything that has existed so far. There will be ethical issues related to the access to these therapies when placed on the market because they cannot be a variant of exclusive treatment for the developed countries. A variant for solving these issues is the development of two payment systems adjusted to the financial strength of different countries. Likewise, the process of development of an autologous gene therapy requires time, the building of labs and resources. Allogeneic therapies might be the solution for the developing countries[14].

> A success model is UK, where the number of studies targeting cell and gene therapies rose from 47% to 73%. The government allocated 70 million pounds to this research area.

12 http://www.pnas.org/content/114/6/1317.abstract
13 https://www.wsj.com/articles/biotech-proposes-paying-for-pricey-drugs-by-installment-11546952520
14 https://www.evaluate.com/vantage/articles/analysis/spotlight/how-pay-gene-therapies-developing-nations

For new technologies to be able to become a reality, a re-assessment of the entire health system is necessary. Steven Pearson, President of the Institute for Clinical and Economic Review, USA: „We need to create a system that will not lead us to stop a high-speed train through a wall".

A successful European model is UK, where the number of studies targeting cell and gene therapies rose from 47% to 73%. The government allocated 70 million of pounds to this research area. 85 clinical trials and 875 pre-clinical trials that evaluate cell and gene therapies are carried out at present[15]. While the number of studies is increasing, the UK is building the infrastructure required for these innovations to continue to develop at the same pace.

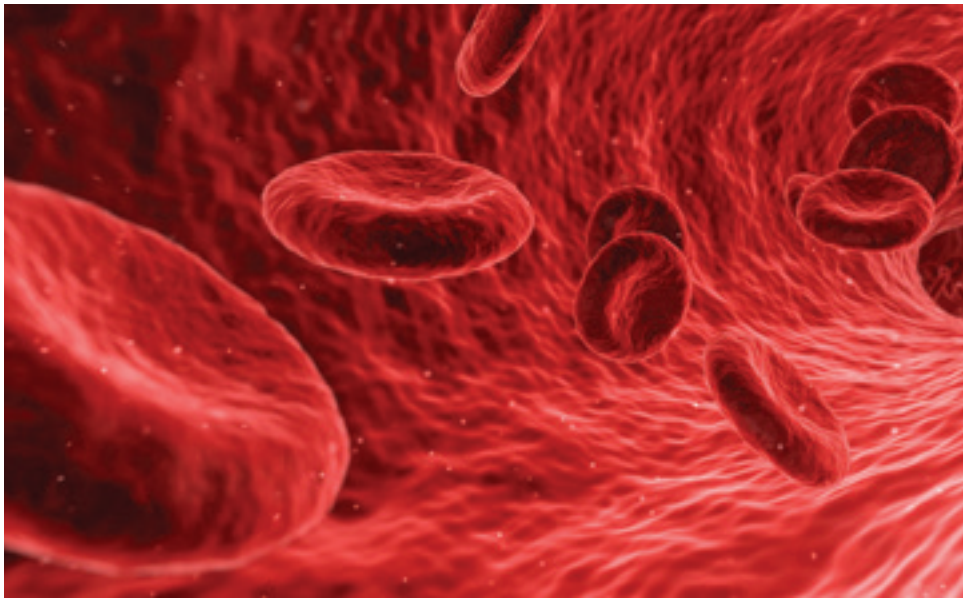
## Recommendations

- Romania should promote a national strategy for genomic medicine, in line with its EU membership, and through the development of the strategic partnership with the USA. We consider that only through a major scientific partnership with the large genomic medicine centers Romania can create its own genomic medicine infrastructure, can shortly establish its own body of specialists trained at the highest level, can re-start medical research and implement genomic medicine in the health system, with benefits for every citizen, but also for the system as a whole.

15 https://ct.catapult.org.uk/resources/cell-and-gene-therapy-catapult-uk-clinical-trials-database

# HEMOPHILIA, GOAL OF "ZERO BLEEDING":
## personalization of treatment, mobile apps, extended half-life products, monoclonal antibodies, gene therapies

### Concept



Hemophilia is a disease that involves disorders of the normal coagulation process, causing extended bleeding, and occurs in two main forms:

80% of the patients have mutations in the gene encoding the factor VIII of coagulation – hemophilia A, and 20% have mutations in the gene for factor IX – hemophilia B. The therapeutic standard for patients with hemophilia A (the most common type of hemophilia) currently is the prophylactic administration of factor VIII. Where this option is not available, the factor is administered when needed („on demand" therapy). However, this prophylactic treatment requires administering an intravenous injection 3 times a week during the entire lifetime, which raises issues of adherence to therapy. Moreover, at global level, only 25 – 30% of the patients with hemophilia have access to the substitution therapy[1].

The past 20 years have seen major progresses in the treatment of patients, turning hemophilia from a life-threatening disease into a chronic disease, but life expectancy continues to be lower than in the general population.

89% of patients claim that pain has a major impact on the quality of life, and 80% consider that hemophilia affects their activity at the workplace[2]. The direct costs determined by frequent hospitalizations and chronic treatment, and the indirect costs of declining productivity, lost working days cause an important burden both for patients and for healthcare systems.

1 https://www.ashclinicalnews.org/features/breakthroughs-gene-therapy-hemophilia/
2 https://www.novonordisk.com/content/dam/Denmark/HQ/aboutus/documents/ChangingHaemophilia/WHD2018/WHD18_Infographic_poster.pdf

The past 20 years have seen major progresses in the treatment of patients, turning hemophilia from a life-threatening disease into a chronic disease, but life expectancy continues to be 15 years lower than in the general population[3].

In March 1994, the World Health Organization said that „Hemophilia will be cured until 2000”. 24 years later we are closer than ever to achieving this goal.

## The present moment

The concept of prophylactic treatment has changed significantly in the light of new approved therapies, and the diversity of treatments is able to contribute to achieving the goal of “Zero Bleeding” in patients with hemophilia.

Major changes have also occurred in the method of administration of the prophylactic therapy and monitoring of patients. In March 2018, FDA approved myPKFiT, the first software that can be used for the personalization of treatment with recombinant antihemophilic factor for patients with hemophilia A. The application allows for a pharmacokinetic curve (PK) for each patient so that to be able to adjust the factor dosage and to customize the administration interval. The pharmacokinetic profile, along with data such as age, weight and other determinations related to the factor activity, result in obtaining therapeutic schemes for each patient. This application also simplifies the testing of patients because only two blood samples are necessary for obtaining the PK curve, as compared to the standard number of 9-11.

In March 2018, FDA approved myPKFiT, the first software that can be used for the personalization of treatment with recombinant antihemophilic factor for patients with Type A hemophilia. The application allows for a pharmacokinetic curve (PK) for each patient, so that to be able to adjust the factor dosage and the administration interval can be customized.

On the other hand, the introduction on the market of antihemophilic factors with extended half-life contributes to the personalization of the treatment and a better control of bleeding by dose adjustment and by increasing the adherence of patients, as a result of administration at a longer interval.

Emicizumab, an artificial protein that mimics the function of coagulation factor VIII, has determined the bleeding to decrease by 79% as compared to prophylaxis with a bypass agent – BPA, and in a study on pediatric population, this determined a reduction of bleeding by 99%. A complication of factor VIII administration is the development of antibodies that decrease the effectiveness of the classical treatment. Emicizumab has a different structure, which means that inhibitors do not develop, but the function of the substance is maintained.

3 http://www.bloodjournal.org/content/110/3/815





The benefits are also related to compliance – the substance is administered subcutaneously once a week – but also a possible reduction of the costs related to hospitalizations, the need for care for complications. Pharmacoeconomic studies show that prophylaxis with this antibody would reduce total costs for patients as compared to BPA and, at the same time, would reduce bleeding by more than 50%. In March 2019, the approval of the medicine was also extended to patients who do not develop inhibitors, being the first new class of medicines for this indication after almost 20 years[4].

Gene therapy is developed as a single dose treatment and has curative potential.

Hemophilia is a monogenic disease and has been considered over the years an important target in the studies aimed at gene therapy. It has been observed that a small increase in the activity of the coagulation factors may have a significant impact on the life of the patients.

By gene therapies, it is intended to obtain a long-term expression of the missing or excessively low coagulation factor and the elimination of substitution treatments. By means of viral vectors, functional copies of the genes for factor VIII or IX are delivered to the patient’s body. One of the safest means to carry genes to cells is via adeno-associated virus (AAV), a technology that was discovered 50 years ago. Most studies aimed at gene therapies for hemophilia use this vehicle.

The results from the first studies assessing gene therapies in patients with hemophilia report sustained values of the coagulation factors even 10 years later. Long-term studies are needed to provide a clear insight into the duration of action of gene therapies for hemophilia, but the term „curative” is justified in this case for several reasons. The patients receiving a gene therapy no longer require substitution treatment with coagulation factor for long period of time, and the bleeding rate is reduced significantly. The studies carried out so far prove results that radically change the quality of the patients’ life.

The results from the first studies assessing gene therapies in patients with haemophilia report sustained values of the coagulation factors even 10 years later. Long-term studies are needed to prove a clear insight into the duration of action of gene therapies for hemophilia, but the term „curative” is justified in this case for several reasons.

In 2014, the first favorable results of gene therapy for hemophilia B were published in the New England Journal of Medicine. Although an increase of only 5% of the factor concentration was achieved, it was noticed that the bleeding episodes dropped by 90% and the response was maintained in time.

At the end of 2017, two other studies published in NEJM showed a revolution

4 https://raportuldegarda.ro/articol/hemlibra-recomandare-aprobare-hemofilie-a-fara-inhibitori/

in the treatment of hemophilia A and B, showing the first encouraging results in the change of the genes encoding the coagulation factors VIII and IX[5]. Bleeding episodes were reduced from 16 per year to less than 1 per year. Likewise, prophylaxis with coagulation factors could also be discontinued and hemorrhagic events were reduced to zero or almost zero.

For hemophilia B, the coagulation factor obtained by genetic engineering is 8 times stronger than normally. The gene is carried to the liver through an adeno-associated viral vector, and the missing coagulation factor is produced there. 9 out of 10 men did not experience any bleeding episode, and in the only case where the administration of the factor was needed, the dose was reduced by up to 91%.

Hemophilia A is 6 times more frequent than hemophilia B, but there have been challenges related to the introduction of the gene into the viral vector because of the increased size of factor VIII. However, solutions were found quickly. No one expected that the gene therapy for hemophilia A would prove efficient so quickly. For 6 out of 7 patients who received high-dose therapy, the level of factor VIII normalized and maintained for up to one year[6].

Gene therapies for hemophilia are still not approved in the European Union.

Personalized prophylaxis with the goal of "Zero Bleeding", and the use of digital solutions, along with access to extended half-life anti-hemophilic factor treatment or with monoclonal antibodies are likely to help maintain the patients' joints unaffected so that they may benefit from gene therapies once they receive marketing authorization.

Personalized prophylaxis with the goal of "Zero bleeding", and the use of digital solutions, along with access to extended half-life antihemophilic factor or with monoclonal antibodies are likely to help maintaining the patients' joints unaffected so that they may benefit from gene therapies once they receive marketing authorization.

## Recommendations

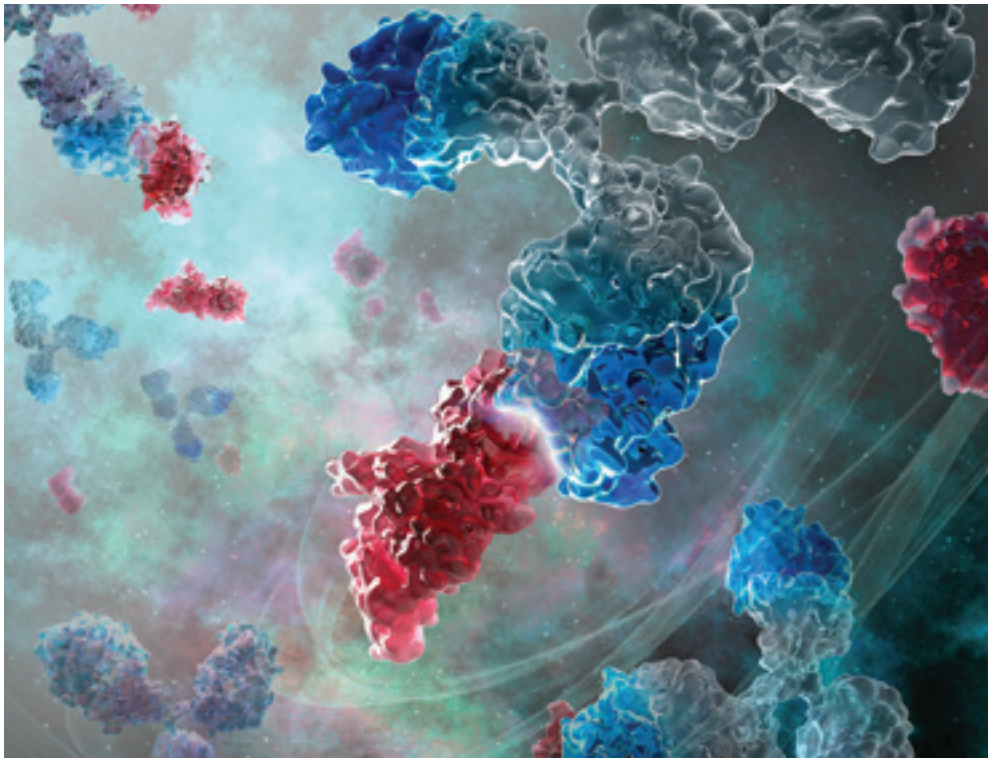
- Promoting the principles of personalized medicine (by using patient-proved applications) under the National Hemophilia Programme
- Setting up a working group in the Health Ministry to achieve a strategy for the access of patients with hemophilia to disruptive innovations (mobile applications for personalization of treatment, monoclonal antibodies, gene therapies)

5 https://raportuldegarda.ro/articol/breaking-news-vindecarea-hemofiliei-a-b-terapii-genice-aproape-realitate/

6 https://www.nejm.org/doi/full/10.1056/NEJMoa1708483

# Biotechnology and biological medicines: value-added for the health system

## Concept



Biotechnology is the basis for manufacturing hundreds of medicines benefiting over 350 million patients worldwide. They are used in the treatment or for the prevention of many serious diseases, including cancer, myocardial infarction, stroke, multiple sclerosis, diabetes, rheumatoid arthritis and autoimmune diseases. These medicines cannot be obtained by chemical synthesis, like conventional drugs, but are produced by living systems (vegetal or animal cells, bacteria, viruses and yeasts). For this reason, the manufacture of biological medicines is much more complex than the manufacture of chemical pharmaceutical products.

Biological medicines are larger and more complex molecules and, that is why, they have greater variability, they have the potential to cause immune reactions, are administered by injections or perfusions and must be transported and stored under special conditions. All new biological medicinal products must follow the centralized procedure, being reviewed by the EMA Committee for Medicinal Products for Human Use (CHMP), which gives a positive or negative opinion, unlike conventional drugs of chemical synthesis, which can be also approved by each Member State. Biological medicines made by other manufacturers after the expiration of the intellectual property protection for the original biological medicine are not exact copies of the reference medicines because their properties are extremely dependent on

> "The safety of the patient is the main criterion for taking therapeutic decisions, and the cost control measures should be achieved through mechanisms that do not interfere with the medical decision"

the cell lines used and the manufacturing process. Therefore, they are not considered to be identical (generic), but similar, being called „similar biological medicines” or „biosimilar”.

## The present moment

A number of biosimilar medicines, with smaller molecules than monoclonal antibodies, are already used in the current medical practice. The European Medicines Agency approved 16 biosimilar medicines in 2017, and at the beginning of 2018, it approved the first biosimilar medicine for the monoclonal antibody bevacizumab, one of the most used medicines for cancer treatment.

Based on this medical practice and knowledge about the development and approval of biological medicines, original and biosimilar, several Romanian professional associations adopted, at the beginning of 2017, a position paper containing a series of essential recommendations for good practice regarding medicines obtained through biotechnology.

The conclusion of the document is that “the safety of the patient is the main criterion for making therapeutic decisions, but the cost-control measures should be achieved through mechanisms which should not interfere with the medical decision”.

The associations of patients in Romania also adopted a position paper regarding the original biological and biosimilar medicines, which identifies 5 essential pillars: continuous information and education, transparency, ensuring access to biological medicines, careful monitoring, maintaining the physician’s decision in choosing the right therapy.

At the beginning of 2018, the American Society of Clinical Oncology (ASCO) wrote a position paper setting the scientific framework regarding the use of biosimilar medicines, also warning that “although in the next years the number of oncological biosimilars available on the market will increase, their impact on the care of patients will depend on the extent to which they are accepted by physicians and patients”.

The Centre for Innovation in Medicine, in partnership with Local American Working Group continued, in 2018, the information, education and policy activities in biotechnology and biological medicines.

In September 2018, on the occasion of the European Biotech Week, the symposium “Value Added of Biotechnology and Biological Medicines in the Romanian Health System” was organized for the first time, thus aligning the Romanian community with the other Member States that marked the moment.





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In February 2019, the Centre for Innovation in Medicine and the Local American Working Group catalyzed the establishment of the Expert Group “Biotechnology and Biological Medicines”, to which 6 professional associations and 5 patients’ organizations adhered with the aim to promote good practice in access to biotechnology and biological medicines in the Romanian health system.

## Recommendations for action

- Adapting the legislative framework (normative acts and methodological norms) to maintain and to consolidate the medical decision regarding the prescription of the biological treatment and regarding the change of treatment, to the detriment of the economic criteria or which are related to the public procurement system
- Increasing the access of the Romanian patients to biotechnology by developing the “Health Innovation” Fund, which will provide the patients with the latest therapeutic methods approved by the European Medicines Agency (EMA) and which are not available yet by the health insurance coverage system in Romania.
- Promoting information and education programmes for the development in the field of competences regarding the prescription of biological medicines and patient management, in those therapeutic areas where the use of biological medicines is still at the beginning.

# DIABETES: major paradigm shift

## Concept

Every 6 seconds a person dies in the world because of diabetes, and every 12 seconds, cardiovascular diseases cause 1 death. At present, 415 million people worldwide suffer from type 2 diabetes and, by 2040, it is estimated that there will be 642 million patients1. The global costs determined by diabetes are estimated to reach 12% of the costs in the health systems. Half of the deaths among diabetics are caused by cardiovascular diseases. According to the American Diabetes Association, two thirds of the patients have high blood pressure, with a two to four times higher risk of death because of heart disease or stroke as compared to healthy persons.

Macrovascular complications are the main cause of mortality, and heart failure is the most frequent of these. Diabetes doubles the prevalence of heart failure. In diabetics, cardiovascular disease develops from a very young age. Likewise, while the patient grows older, the mortality rate from cardiovascular causes also increases.

A study carried out by the Centre for Innovation in Medicine and IMAS in 2016 showed that, in Romania, diabetes is perceived by the general population as being as severe or worse a diagnosis than heart disease or obesity.

The term diabetes includes chronic metabolic diseases that have hyperglycemia in common. However, the high levels of glucose are multifactorial. Today, we understand better the complex mechanisms that determine a decrease in insulin production or its low effectiveness. Type 1 diabetes appears through an interaction between the gene susceptibility, immunologic and environment factors. Type 2 diabetes is a clear example of multifactorial, polygenic disease. Likewise, there are more and more methods

In order to discuss about personalized medicine in diabetes, it is necessary to redefine the disease, according to new research.





to quantify the impact of these factors on the body. The heterogeneity of the disease suggests the need for a clearer classification for correct identification of the individuals who are prone to complications and, especially, for the individualization of the therapy.

## The present moment

In order to discuss about personalized medicine in diabetes, it is necessary to redefine the disease, according to the new research.

A study published in Lancet, in March 2018, suggests that the current classification of diabetes is simplistic and identifies 5 forms of the disease: 3 severe forms of diabetes and 2 mild forms, which differ genetically and phenotypically2. One corresponds to type 1 diabetes, while the others can be considered sub-types of the type 2 diabetes. The difference between them might have significant implications in medical practice and might change the definition of diabetes. Many patients receive medicines which they do not need, and others are not treated properly even since they are diagnosed. The biomarker testing, assessment of genotypes and calculation of the genetic risk scores are expected to contribute to this classification.

Likewise, the diagnosis and monitoring methods of diabetes are re-assessed. Since the introduction of glycosylated hemoglobin (HbA1c) in 2010 as a diagnostic test, there is a tendency for physicians to rely only on these values. HbA1c is a practical test, but the new studies show that it does not diagnose the diseases as well as the previous oral glucose tolerance test. 73% of the diabetes cases can be omitted if the diagnosis is based only on the values of glycosylated hemoglobin and many patients who might benefit from early interventions are not diagnosed on time3.

The personalization of the diabetes treatment was the core concept based on which a consensus was achieved between the American and European guidelines in diabetology. In October 2018, on the occasion of the Annual Meeting of the European Diabetes Association (EASD 2018) the ADA-EASD (American Diabetes Association and European Association for the Study of Diabetes) Consensus was presented, and the conclusion made by one of the co-authors of the report, Professor Chantal Mathieu, PhD, was the following: „We must evaluate the patient’s characteristics and take into consideration specific factors that will influence the choice of treatment, and then we should outline a plan in agreement with the patient”.

**415**

million people worldwide suffer from type 2 diabetes and by 2040, it is estimated that there will be 642 million patients.

The new anti-diabetic medicines provide a cardiovascular protective effect independent of the glucose control, and the major international guidelines recommend their introduction in the practice of cardiologists. Two new classes of medicines for the treatment of type 2 diabetes have shown a significant benefit in the reduction of cardiovascular events, apart from the hypoglycemic effects: sodium glucose co-transporter inhibitors (SGLT2) and glucagon-like peptide 1 receptor agonists (GLP-1). The ADA and EASD guidelines recommend SGLT2 inhibitors as the first therapeutic class for diabetic patients with heart failure and/or chronic kidney disease. Dapagliflozin (a SLGT inhibitor) was the first oral adjuvant therapy approved in Europe for patients with type 1 diabetes, in March 2019. Clinical trials also show that liraglutide, a GLP-1 agonist, used as additional treatment to insulin therapy in patients with type 1 diabetes, may reduce the level of glycosylated hemoglobin (HbA1c) and systolic blood pressure4.

Diabetology should be in the training of a cardiologist, as the assessment of the cardiovascular risk should be a concern for the diabetologist from the first examination of the patient.

In 2018, we witnessed another consensus, this time an interdisciplinary one: for the first time, the recommendations of the American Diabetes Association were aligned with those of the American College of Cardiology regarding the management of cardiovascular risk in patients with type 2 diabetes.

Diabetology should be in the training of a cardiologist, as the assessment of the cardiovascular risk should also be a concern for the diabetologist from the first examination of the patient.

Another important moment which actually shows the pace of scientific advancement was the ADA decision to update in real time the Standard of Care guideline. Only 4 months after its publication, on 27th of March 2019, the guideline included recommendations for medication targeting cardiovascular risk5. Three sections of the guide were modified based on a study presented at the end of 2018, which showed the benefits of the SGLT2 inhibitor, dapagliflozin, in reducing hospitalizations for heart failure and in decreasing the advancement of the chronic kidney disease.

Other recommendations referred to the effectiveness of a synthetic derivative of Omega 3 fatty acids which reduce the risk of ischemic events in patients with hypertriglyceridemia and high cardiovascular risk.

The first guideline was published in 1989 and had a total number of 4 pages. 28 years later, an updated version of the guide has over 170 pages.





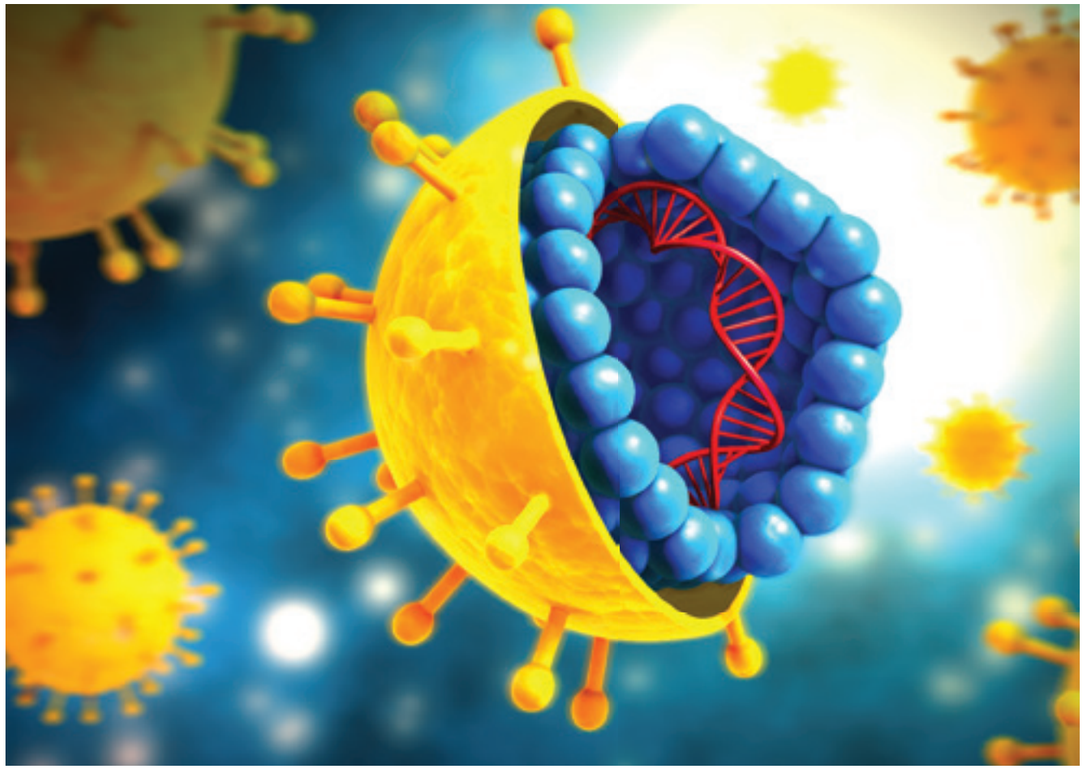
Starting with 2005, over 40 new therapeutic options for type 2 diabetes were approved. New medicines and technologies for diabetes control are developed at an unprecedented pace, so that the annual update of the guidelines has proved to be ineffective. The new changes must be included in the guidelines while they appear and communicated in real time. From the beginning of this year, ADA has decided to review the recommendations in the guideline right at the moment of the publication of the new studies or the approval of new medicines and not at the end of the year, as it was done previously. Due to this dynamic character, the guideline is also called „Living Standard of Care”.

## Recommendations

- Establishing a multidisciplinary working group at the Ministry of Health to develop an innovative short, medium and long-term strategy to reduce the burden of diabetes through control and integrated approach of risk factors for disease and for complications
- Priority update of the guideline and management protocols of diabetes in Romania, in accordance with the ADA-EASD Consensus, and creating a real-time update mechanism. Implementing therapeutic protocols for all anti-diabetes oral medicines so that to develop a unitary practice aligned to international treatment standards and disease management
- Implementing a national diabetes plan to include early screening and diagnosis, assessment of cardiovascular-renal-metabolic risk, in accordance with the principles of the ADA-EASD Consensus
- Establishment of a national registry of patients with diabetes, along with promoting the Electronic Patient File of persons with diabetes
- Promoting information and education activities for physicians, patients and general population about the paradigm shift in diabetes.

The conclusion made by one of the co-authors of the report Professor Chantal Mathieu, PhD:
“We must assess the patient’s characteristics and take into consideration the specific factors that will influence the choice of treatment, and then we should outline a plan in agreement with the patient”.

# ELIMINATION OF HEPATITIS C: from medical stage to societal approach



## Concept

Interferon-free treatments have become the gold standards for Hepatitis C in the past years. Interferon-free treatments have proved to be more effective and safer over a short period of time than conventional therapies for most of the patients with Hepatitis. C. The new generation of drugs target directly the Hepatitis C virus. C. Although the costs of interferon-free therapies were initially considered to be very high, questioning the financial sustainability of the use of new treatments in health



2019 “STATE OF INNOVATION” REPORT

systems, the cost of therapies are currently decreasing, while each state negotiated its own price, and the number of medicines available on the market is on the rise.

In this context, the focus is on the strategies to eliminate Hepatitis C. In 2017, the World Health Organization launched the first global strategy to eliminate hepatitis from the public health issues until 2030. The WTO initiative is aimed in particular at the infections with Hepatitis B and Hepatitis C virus. Despite the WTO recommendations, many countries still do not have national registries and plans for Hepatitis C, which are considered a prerequisite for achieving the objective to eliminate the disease.

## The present moment

Over 25,000 Romanian patients with Hepatitis C have benefited from access to interferon-free treatment until now, as a result of the conclusion of several cost-volume-outcome contracts. The success rate exceeds 98%. In April 2019, the National Framework Plan for the control of Hepatitis B, C and D was launched. Regarding screening for Hepatitis D, the Ministry of Health announced the initiation of such a programme, using European structural funds.Recomandări pentru acțiune

- Implementing the National Framework Plan for the control of viral hepatitis. For Hepatitis C, we recommend a distinct method of purchasing interferon-free therapies, under multiannual contracts, as a fundamental element in achieving the goal of eliminating Hepatitis C until 2030. At the same time, we recommend switching the focus to society as a whole, in order to raise awareness, to inform and to educate about Hepatitis C, thus creating the proper context for achieving the goal of eliminating Hepatitis C in Romania.

Over 25,000 of Romanian patients with hepatitis C have benefited from interferon-free treatment until now, as a result of the conclusion of several cost-volume-outcome contracts. The success rate exceeds 98%.

# DIGITAL MEDICINE: development of a national strategy in the European context

## Concept

Digital medicine (health) designates an emerging field at the confluence of the digital environment and genomic technologies, on the one hand, with health, healthcare system and society as a whole, on the other hand. The goal of digital medicine is to increase the efficiency of the healthcare systems through a more personalized approach to prevention, early detection, diagnosis and treatment. Digital medicine requires the use of ICT means to solve the individual situations of each patient, and certain issues in the healthcare system. These ICT technologies include the hardware and software component and the service component, and a few concepts have already begun to materialize: telemedicine, mobile phone applications, sensors that can detect vital signs, artificial intelligence, blockchain technologies, development of computational analysis techniques, Big and Smart Data, virtual patient, in silico clinical trials, etc.

## The present moment

In the autumn of 2017, during the Estonian Presidency of the Council of European Union, “Digital Health Society Declaration” was launched, which aims to contribute to the development of digital medicine in Europe by a structured approach in 4 fields: interoperability of health systems, ownership of medical data, free movement of the medical data in the European Union, monitoring of the impact on initiatives on health systems to identify best practices.

In April 2018, the European Commission launched to the Member States the invitation to sign the Declaration of Interest Policies for cooperation in three areas associated with digital medicine: artificial intelligence, blockchain technologies and personalized and genomic medicine. These add to other initiatives to which the European Commission invited to participate, on a voluntary basis, the Member States (such as eHealth Network).

In April 2018, the European Commission launched to the Member States the invitation to sign the Declaration of Interest Policies for cooperation in three fields associated with digital medicine, artificial intelligence, blockchain technologies, and personalized and genomic medicine.

At the level of the European Union, a number of projects are under way, aimed at achieving the virtual “twin” of the human brain, of some types of cancer or even of the entire human body, and projects whose purpose is to define the new generation of clinical trials, based on digital medicine.

Romania has begun to adjust the legislation in digital medicine, by adopting a Government Emergency Ordinance, at the beginning of 2018, which defines the legal framework for setting up the national registries and for the operation of rural telemedicine and medical telemedicine. The announced establishment of the agency for e-Health and of the national disease registries, by using European funding, have the potential to contribute to the structuring and development of the field in Romania.

## Recommendations for action

- We recommend the achievement of a National Strategy for e-Health, as a fundamental goal of the e-Health Agency (announced to be established in 2018), as a basis for the development of the public health system, but also to ensure the structured involvement of the private partners and communities interested in digital medicine in the whole country.

At the level of European Union, a series of projects are under way, aimed at achieving the virtual “twin” of the human brain, of some types of cancer or even of the entire human body.



2019 “STATE OF INNOVATION” REPORT

# Innovative medicines approved by EMA from 1st January 2018 – 30th April 2019

| Therapeutic area / Name of medicine | Therapeutic area / Name of medicine |
|---|---|
| **Oncology** | |
| Alunbrig (brigatinib) | Treatment of adult patients with advanced non-small-cell lung cancer (NSCLC), ALK positive, previously treated with Crizotinib |
| Braftovi (encorafenib) | Metastatic or unresectable melanoma, BRAFV600 positive |
| Erleada (apalutamide) | Non-metastatic castration-resistant prostate cancer |
| Imfinzi (durvalumab) | Inoperable locally advanced NSCLC for adult patients whose tumors express PD-L1 in ≥ 1% of tumor cells |
| Kymriah (tisagenlecleucel) * | B cell acute lymphoblastic leukemia, diffuse large B-cell relapse or refractory lymphoma |
| Mektovi (binimetinib) | Metastatic or unresectable melanoma, BRAFV600 positive |
| Nerlynx (neratinib) | HER2 positive breast cancer in patients previously treated with Trastuzumab |
| Poteligeo (mogamulizumab) | Mycosis fungoides, Sezary syndrome |
| Rubraca (rucaparib) | Recurrent ovarian epithelial neoplasm of the fallopian tubes or recurrent primary peritoneal neoplasm |
| Verzenios (abemaciclib) | Advanced or metastatic breast cancer, HR+, HER- |
| Yescarta (axicabtagen ciloleucel)* | Diffuse large B-cell relapse or refractory lymphoma (DLBCL) and large primary mediastinal B-cell lymphoma (PMBCL) |
| **Infectious diseases** | |
| Alpivab (peramivir) | Treatment of uncomplicated influenza in adults, teenagers and children from the age of 2 |
| Biktarvy (bictegravir, emtricitabine, tenofovir alafenamide) | Treatment of adults infected with human immunodeficiency virus type 1 (HIV-1) without evidence of viral resistance in the class of integrase inhibitors, emtricitabine or tenofovir |
| Delstrigo (doravirine / lamivudine / tenofovir disoproxil fumarate) | Treatment of adults infected with human immunodeficiency virus type 1 (HIV-1) |
| Pifeltro (doravirine) | Treatment of infection with virus type HIV-1 in adults, without evidence of resistance to compounds of the INNRT class |
| Vabomere (meropenem & vaborbactam) | Complicated urinary tract infections, including pyelonephritis/complicated intraabdominal infection/Hospital acquired pneumonia |
| Xerava (eravacycline) | Treatment of complicated intraabdominal pneumonia (IIAc) in adult patients |
| **Neurology** | |
| Aimovig (erenumab-aooe) | Migraine prophylaxis in adults with migraines at least 4 times a month |
| Emgality (galcanezumab-gnlm) | Migraine prophylaxis in adults with migraine at least 4 times a month |
| Onpattro (patisiran) | Transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy |
| Rxulti (brexpiprazole) | Treatment of schizophrenia in adult patients |
| Tegsedi (inotersen) | Treatment of polyneuropathy in stage 2 or 3 in adult patients with hereditary transthyretin amyloidosis (hATTR) |
| **Hematology** | |
| Besremi (ropeginterferon alfa-2B) | Polycythemia vera without symptomatic splenomegaly in adults |
| Cablivi (caplacizumab) | Acquired thrombotic thrombocytopenic purpura (PTTd) |
| Hemlibra (emicizumab-kxwh) | Routine prophylactic treatment in patients with hemophilia A with inhibitors with factor VIII and in patients with severe haemophilia A without inhibitors |
| Jivi (damoctocog alfa pegol) | Treatment and prophylaxis of hemorrhages in previously treated patients with hemophilia A aged ≥ 12 years |
| Lusutrombopag Shionogi | Treatment of severe thrombocytopenia in adult patients with chronic liver disease following invasive procedures |
| Mylotarg (gemtuzumab ozogamicin) | Acute myeloid de novo, CD33 positive, previously untreated leukemia (AML) |
| **Immunology/Reumatology** | |
| Ilumetri (tildrakizumab) | Treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy |
| **Endocrinology** | |
| Lamzede (velmanase alfa) | Treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis |
| Macimorelin | Diagnosis of growth hormone deficiency (GHD) in adults |
| Mepsevii (vestronidase alfa-vjbk) | Treatment of non-neurological manifestations of mucopolysaccharidoses VII (MPS VII, Sly Syndrome) |
| Myalept (metreleptin) | Substitution therapy in patients with leptin-related complications such as generalized or acquired congenital lipodystrophy |
| **Metabolic disorders** | |
| Segluromet (ertugliflozin & metformin HCl) | Type 2 diabetes as an adjunct to diet and exercise to improve glycemic control |
| Steglatro (ertugliflozin) | Type 2 diabetes as an adjunct to diet and exercise to improve glycemic control |
| Steglujan (ertugliflozin & sitagliptin) | Type 2 diabetes as an adjunct to diet and exercise to improve glycemic control |
| **Pneumology** | |
| Symkevi (tezacaftor / ivacaftor) | Treatment of patients with cystic fibrosis with mutations in both copies of CFTR gene |
| Takhzyro (lanadelumab-flyo) | Routine prevention of recurrent episodes of hereditary angioedema (HAE) |
| **Vaccines** | |
| Dengvaxia | Prophylaxis of Dengue disease determined by 1, 2, 3 and 4 serotypes of Dengue virus |
| Shingrix | Prevention of herpes zoster (HZ) and post-herpetic neuralgia (PHN) |
| **Gastroenterology** | |
| Rizmoic (naldemedine) | Treatment of opioid-induced constipation (OIC) in adult patients who were previously treated with a laxative |
| **Oftalmology** | |
| *Luxturna (voretigene neparvovec) | Treatment of adult patients, children and adolescents with loss of vision because of hereditary retinal dystrophy, caused by confirmed RPE65 biallelic mutations, and who have a sufficient number of viable retinal cell. |
| *ATMP | |

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**“State of the Innovation”** is the annual report of the Centre for Innovation in Medicine for the political environment in Romania.

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# State of innovation

2019