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Perspective

Current trends of digital solutions for diabetes management

Maryna Neborachko [a, *], Aleksandr Pkhakadze [a], Iryna Vlasenko [b]

[a] Digital Health Expert Group, Public Association "Hi-Tech Office Ukraine", Ukraine
[b] Department of Pharmaceutical Technology and Biopharmacy, National Medical Academy of Postgraduate Education, Ukraine

A B S T R A C T

Industry 4.0 is an updated concept of smart production, which is identified with the fourth industrial revolution and the emergence of cyber-physical systems. Industry 4.0 is the next stage in the digitization of productions and industries, where such technologies and concepts as the Internet of things, big data, predictive analytics, cloud computing, machine learning, machine interaction, artificial intelligence, robotics, 3D printing, augmented reality.

As an area of therapy with the best market potential and one of the most expensive global diseases, diabetes attracts the best healthcare players, who use innovative technologies.

Current trends in digitalization of diabetes management are presented.

Some stages in the development of diabetic care.

1776 - determination of glucose in urine by taste
1900 - creation of test strips for determination of glucosuria
1922 - creation of insulin
1955 - the first plastic syringes
1977 - the appearance of glucometers
1978 - the first insulin pumps
1985 - NovoPen pen injector
1993 - intensive insulin therapy
1999 - Aspart is analog of insulin
1999 - long-term glucose monitoring system
2013 - digital multisided platforms
2013 - wireless sensors
2016 - implantable sensors
2016 - smart insulin
2017 - artificial pancreas
2017 - virtual reality
2017 - deep machine learning and AI
2018 - Big Data analysis

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In 2017, the digital funnel has undergone certain changes. Conservative medicine and pharmaceuticals are now placed together at 13th place (compared to 9th and 12th places in 2015 respectively) [1].

1. Picture 1

Digitalization of the medical industry, like any other, is not a matter of choice, but a matter of time. A large number of impressive digital medical services are already on the market. The direction of the combination of sensory solutions and digital products for the subsequent provision of service to the user seems to be quite universal. Such sensors as ultrasonic sensors and even MRI can move beyond hospitals, as glucometers did in their time. Sensors that will be built into everyday things such as mirror, floor, clothing, in the future, nanosensors, neurosensors and implanted sensors will no longer excite our imagination, but are a logical continuation of existing developments.

The implementation of voice messengers and chat bots, the widespread use of artificial intelligence, deep machine learning, the results of analysis of the accumulated BigData, gene therapy and nanotechnology solutions and the engagement of virtual reality technologies is our near future. At the same time, the assistance will be maximally personalized. For example, the FDA has already approved the first digital tablet - AbilifyMyCite [2]. Solutions based

* Corresponding author.
E-mail address: maryna.neborachko@ht-office.org (M. Neborachko).

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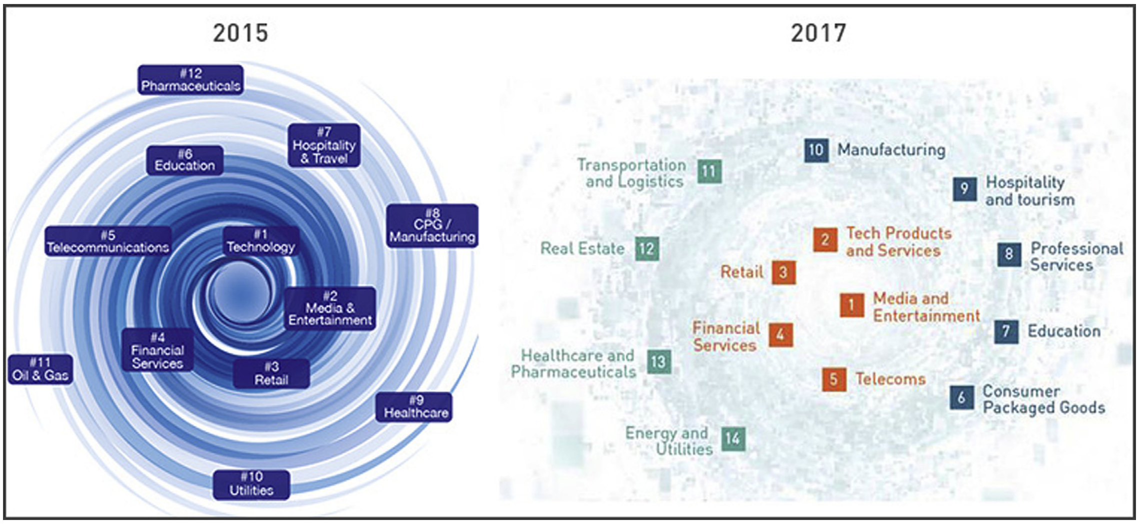


Picture 1. Current Digital Vortex (1).

on artificial intelligence and machine learningxbird [3] is said that it will save 1 million lives by 2020.

Therapeutic training and training of medical specialists also become more effective through the implementation of digital projects. A successful example of online education for specialists was the International Diabetes Federation (IDF) system for the training of medical workers and specialists in the field of diabetes - IDF Diabetes School [4].

1.1. Regional trends

A number of countries are currently taking steps to create databases in the field of bioinformation and, in the future, the creation of innovative ecosystems in cooperation with different sectors.

In February 2018, the South Korean government [5] announced its decision to consolidate medical data from hospitals throughout the country and create a comprehensive database to promote the lucrative fields of the country's pharmaceutical industry and public health.

The goal of this step is to create about 35,000 new jobs in the growing biotechnology and healthcare sector and increase the market share of South Korea in the world sector by 2022 from the current 1.8% to 4%.

According to officials, in the first half of this year it is planned to collect genetic and biometric data about 10 million people to create a bioinformational database.

The Big Data will be used to research and develop new medicines, to predict the underlying diseases and to identify unusual symptoms in vulnerable groups on medical grounds.

Once the initial database settles in, the government will seek to expand its capabilities through cooperation with various sectors, such as automobile, telecommunications, information technology and cosmetics.

As an example, we can take a biosensor that should be installed in cars. These sensors can detect unusual symptoms of the driver's health and, if necessary, contact emergency call centers.

In addition, from 2020, it is planned to launch a pilot project on reasonable urban health care, which will provide citizens with a comprehensive service based on personal information about health, weather and environmental factors.

The project on consolidation of medical data with the possibility of further analysis is also being developed in Israel.

In March 2018, Israel approved a plan [6] on investment of 1 billion shekels (275 million US dollars) to digitalize personal data about the health status of nearly 9 million citizens, what should help in the development of new medicines.

The government of the country in partnership with the German software giant SAP SE plans to collect information from Israeli volunteers and create a database for academic purposes and for foreign medical companies. The data can be used for preventive medical events and development of personalized care.

Israeli doctors have been documenting patient data on digital platforms for many years and will now be able to access clinical data from more than 98% of the population.

The government of Israel expects that the plan will attract foreign investment and will stimulate partnerships with local entrepreneurs.

The project on consolidation of genomic information is developing in Europe.

13 European countries signed a declaration [7] on granting cross-border access to their genomic information. This initiative changes the rules of the game for European research in the field of health and clinical practice: the exchange of genomic data will improve understanding and prevention of diseases and will allow the development of personalized treatment (and targeted use of medicines), in particular, for rare diseases, brain diseases and cancer.

1.1.1. Similar projects take place in other countries

As early as 2015, MIT Review [8] reported that a genetic company in Iceland, named DeCode Genetics, collected complete DNA sequences for 10,000 people. And since the population of Iceland has about 320,000 citizens, and they are quite closely related, it is expected that it is possible to extrapolate this data to the DNA composition of almost the entire population of the country, including those who have never participated in this research.

In March of this year, Estonia announced the launch of the first stage of the national state genetic testing [9], in which 100,000 of its 1.3 million citizens received information about their genetic risk for certain diseases.

In April, there was information that Blockchain would provide a DNA database for 50 million citizens in the eighth largest state in India [10]. The government of the country signed a Memorandum of Cooperation with Shivom, the German startup of genomics and precision medicine, who announced the launch of a pilot project.

This step is consistent with the general trend of growing interest in population genomics and, at the same time, the tendency to protect confidential data through a block chain.

The trend towards the development of this direction will persist throughout the world and it is supposed [11] that by 2025, from 100 million to 2 billion human genomes will be sequenced.

Technologies using artificial intelligence (AI) are becoming one of the leading trends in business and everyday life and, undoubtedly, find their reflection in medicine.

The leading areas of application of AI [12] are automation with use of robotics, rebuilding of mobile application development, machine learning, cybersecurity, voice messengers and Big Data analysis.

Last year, investors invested more than $ 15.2 billion in financing AI startups in various industries. This was a 141% splash in funding compared to 2016 [13].

A number of countries are taking serious steps to introduce this technology. Despite the fact that the United States remains one of the leading leaders in this field, countries such as China will seriously compete for the introduction of AI technologies.

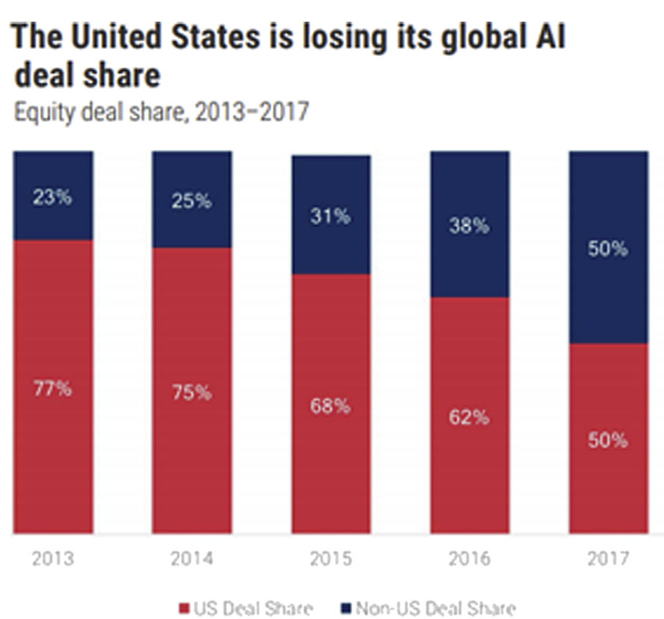
In July 2017, the Chinese government announced that it plans to reach the United States level in the field of artificial intelligence by 2020 and become the world leader by 2030 [13].

In 2017, artificial intelligence start-ups in China [13] accounted for 48% of all capital investments going to AI startups worldwide, which is more than in the US. In deep training, China publishes six times as many patents as the US.

2. Picture 2

The EU is seriously concerned about the existing gap in the development of these technologies between Europe, the US and China. The group, called the Joint European Disruption Initiative (JEDI), which consists of 117 experts from academic circles and industry, believes that Europe can become “inappropriate” in the modern world of applied technologies if it does not double its efforts in R&D.

JEDI propose to EU countries to establish a fund of $ 1.2 billion to support the pan-European research and development movement [14].



Picture 2. AI Global deals 2013–2017 (13).

At the end of March this year, French President Emmanuel Macron announced that his government would spend $ 1.5 billion on a number of initiatives to increase researches in the field of AI in France as part of efforts to help the country bridge the research gap that exists between Europe, the USA and China [15].

2.1. Digital services for people with diabetes

Management of diabetes mellitus is considered as a model for helping patients with chronic non-infectious diseases, resulting in a significant number of proposals in the digital market devoted to solving any problems associated with diabetes.

The tasks of diabetes mellitus management, which can be solved with digital solutions, are therapeutic training, maintaining of the motivation to comply with recommendations on diets and exercises, control and self-control of the disease, personalized approach to each person, support of the diabetic team at all stages of the life of a person with diabetes, prevention of development of the disease complications and maintaining the quality of life of people with diabetes.

According to review data on the use of technologies in the field of education and support for people with diabetes, which were published between January 2013 and January 2017, digital solutions for self-monitoring of diabetes mellitus significantly improve the level of glycated hemoglobin [16].

WellDoc (the digital platform for people with diabetes) [17] and Glooko digital platform, with which all leading glucose sensors and insulin pumps can be synchronized [18], remain leaders in the field of digital diabetic care, as well as a successful example of the rapid development of digital service - the MySugr project, which, thanks to its acquisition by Roche company, has passed from 50,000 downloads of the mobile application to more than 1 million downloads and clinical studies of its own effectiveness [19,20] in a year.

2.2. Insulin pumps, glucose monitoring systems and closed systems

Digital solutions in the field of help for people with diabetes are already inextricably linked with insulin injection systems, long-term glucose monitoring systems and with combined solutions - closed-loop cycles of “measurement-injection" type.

The acquisition of wireless data on the operation of insulin pumps on mobile devices has already become a standard: data from the pump are loaded into the analytic program; access to the pump via the Internet (which is particularly convenient in pediatrics) is possible, access for physicians to the pump data with the possibility to reconfigure the injection scheme.

A number of clinical studies have already been carried out, and a significant evidence base for the effectiveness of the use of these systems for more effective disease control has been accumulated [21–33].

News from companies that manufacture glucose monitoring systems, insulin pumps and closed systems as a whole are come to attempts to reduce the size of sensors, reduce the number of necessary calibrations, extend the service life of one sensor and increase its accuracy.

So, Dexcom introduced the Next-Gen G6 Sensor with the ability to use it up to 10 days instead of 7, with one calibration measurement per day, reduced by 30% with a transmitter with improved accuracy and reliability, and new alert functions. It is separately emphasized that the effect of acetaminophen (Tylenol) on the results of the sensor has been eliminated. The application to the FDA wasfiled in 2017 and in April of this year, the approval of this organization has already been received [34]. AlsoDexcom in partnership with Verily (previously Google Life Sciences) is working on miniaturization of the transmitter, with the possibility of using it for 14 days without calibration, with product development to a disposable device as big as M&Ms candy (it is expected in 2020/21) [35].

Medtronic introduced last year the Minimed 670G, the precursor of the artificial pancreas, using the latest Guardian 3 CGM sensor, whose mass production was delayed because of adverse weather conditions in Puerto Rico last year. The company also announced Sugar. IQ, a mobile application using IBM Watson analytics to identify trends in the treatment of diabetes, and offer the user personalized tips for improving the delivery of care to diabetes in real time [36].

The company Becton Dickinson in 2018 plans to launch Patch Pump for people with type 2 diabetes - a fully disposable device which can be used for 3 days for basal and bolus input modes, and is also working on the creation of Smart Pen Needle Technology - a needle for all types of insulin pens that will report the injected dose thanks to the Bluetooth module [37,38].

Clinical studies of the original Closed Loop solution have begun: iLet4 system from Beta Bionicsis the fourth generation of a closed cycle with a double content of hormones - glucagon and insulin with an emphasis, in particular, on the stability of the glucagon formula [39].

The planned clinical trials of a closed cycle of insulin delivery based on the Bigfoot Loop insulin pump fromBigfoot Biomedicaland smart pen injector with the automatic titration functionBigfoot Inject (Timesulin) [40].

t: slim X2 Pump from company Tandem Diabetes Care has a system for stopping insulin delivery in the face of hypoglycemia - Low Glucose Suspend (PLGS) System. Hybrid closed system operates on the basis of the Dexcom sensor using TypeZero algorithms - the launch of the product pre-announced on H1 2019 [41].

Contour. Next ONEis a mobile virtual reality application for visualization of a glycemic curve based on measurements with a connected glucometer that visualizes the obtained measurement result with the corresponding color signal similar to traffic light in comparison with the target glycemic values. Currently on Google Play: 10,000−50,000 downloads, V.1.3.11 of 19.09.2017 [42].

The Eversense® Continuous Glucose Monitoring System from Senseonics, Inc. is the first and only CGM with an implantable sensor that can be used up to 90 days: implanted under the skin thanks to a 5-min surgical manipulation and allows for 90−180 days to receive measurements of the level of glycemia before the need to replace it with a new one. Above the implantation site is a transmitter on the skin that transmits data to the mobile application. It can be removed and returned to its place. The system requires calibration 2 times a day. It is available in 13 countries, but not yet in the US [43].

MEDTRUMcompany presented the original solution - one-time CGS6 EasySensesystem [44].

Roche company stopped selling insulin pumps in the US. The company will return with a closed system. A partnership with Senseonics has been concluded to use the Eversense sensor. The company purchased the mySugr project to create the basis for its own digital platform. Now the mobile application is sold together with the Accu-Chek Connect glucometer. On Google Play, the number of downloads indicated as 500,000−1,000,000 (1,5 years ago there were 10,000−50,000 downloads). Features of the application, which we noted in the previous review, even before the partnership with Roche: easy and personalized interface (diet, medication, carbohydrate intake, nutrition, blood glucose levels and much more) with clear glycemic level diagrams; motivational changes and feedback, for type 1 and 2 diabetes; daily, weekly and monthly data analysis; secure backup of data. At the same time, the solution is integrated withGoogle. Fit, through which data on distance, activity, blood pressure, CGM data, weight is available. mySugr Pro can be activated for free with some Accu-Check® devices when ordered (free of charge) through mySugr or with a monthly ($ 2.99) or annual subscription ($ 27.99). USA). Also, the smart search is offered: search for dining places, insulin calculator (only for EU), generating reports in PDF and Excel formats; system of reminders; the ability to make and store food photos (attaching photos of dishes to simplify the calculation of carbohydrates). In this case, this solution has already proved its effectiveness in a clinical study: the level of glycosylated hemoglobin in 440 patients with type 2 diabetes and initial level of more than 8% decreased by 1.3% in 6 months of mySugr use [45].

2.3. Fitness and diabetes

Last year, information appeared that FitBit is investing $ 6 M in the development of long-term monitoring of glycemia. Of course, Apple is also working in this direction to directly implement such a system in Apple Watch, but, as always, under a lot of secrecy [46,47].

In 2015, Medtronic entered into an agreement with Samsung to develop a project to create a smart watch with an integrated sensor for the detection of glycemia, but there is still no data on the practical implementation of the idea [48].

Dexcom announced a partnership with the manufacturer of fitness trackers Fitbit to develop a product for people with diabetes. The first project is the redirection of data from Dexcom G5 to new Fitbit smart watches (the project was purchased from Pebble) [49]. Of course, there are rumors about the direct transfer of data Dexcom-to-Apple Watch.

2.4. Artificial intelligence and diabetes

According to a study by mHealth App Economic 2017, 68% of developers of mobile applications for mobile applications and publishers believe that diabetes is still a therapy area with the best market potential for digital health care solutions in the near future, and 61% is artificial intelligence by the most breakthrough technology, which forms the sector of digital health [50].

As an area of therapy with the best market potential and one of the most expensive global diseases, diabetes attracts the best healthcare players, as well as beginners, who use innovative technologies and AI to solve everyday problems faced by people with diabetes.

The treatment of diabetes largely depends on the type of diabetes and its severity. Breakthroughs in AI will continue, as technology becomes more developed, and this will further increase the development of breakthrough mobile solutions for diabetes and the health sector.

A number of studies have been carried out which show that artificial intelligence can be a useful tool that can be used to manage and prevent diabetes mellitus. In particular, a research published in Medical Internet Research journal showed that people at risk of developing type 2 diabetes who used Lark Health Loss Health Coach AI managed to reduce their weight by 2.38% of their baseline and increase the percentage of healthy food [51].

Solutions created with use of artificial intelligence and deep machine learning were presented during the last congress of the European Association for Diabetes Mellitus (Lisbon, Portugal) - ID-x and Eyenuk. As a continuation, in April 2018, there was an information that FDA stated that it would allow the sale of the first medical device with artificial intelligence (AI) software to detect diabetic retinopathy: The IDx-DR device produced by IDx LLC is the first to obtain permission to use the screening solution, without the need for the clinician to interpret the image or results. This makes it suitable for use by healthcare providers who are not specialists in the field of ophthalmology, such as primary care physicians, who interact with patients with diabetes the most frequently [52].

In December 2017, Cellnovo company announced the launch of the PEPPER (Patient Empowerment through Predictive Personalized decision support) clinical study on the use of AI for management of Type 1 diabetes [53].

The main market players for using AI in the field of diabetes are such companies as:

Bigfoot Biomedical uses artificial intelligence to develop systems designed to automatically and continuously optimize the delivery of insulin to people living with diabetes [54].

DIABNEXT® is the first A.I. diabetes that enables unique personalized metric analysis and provides decision-making tools for physicians and patients, helping in management of both prediabetes and diabetes [55].

DreaMed Diabetes is dedicated to expanding the capabilities of insulin-dependent patients and their physicians with innovative and patient-oriented decision support technology. The first company in the world that received CE Mark approval for artificial pancreas technology [56].

Hedia is a personal diabetes assistant based on artificial intelligence. It gives recommendations for a diet and takes into account physical activity and recommendations for choosing an insulin dose [57].

MedicSen are prediction modules which helps patients with diabetes to make decisions taking into account potential risks. The algorithm predicts the future values of glucose for 1 h ahead. Their chat-bot interface can send verbal (voice) or written messages [58].

TypeZero combines next-generation data transfer technologies, proven metabolic models and modern engineering practices to develop specialized analytics tools and solutions for monitoring blood glucose levels to help people with diabetes to control their disease [59].

xbird is their solution which controls personal, environmental and behavioral digital biomarkers, using artificial intelligence and machine learning for millions of data points with the final result, creating effective solutions for physicians and patients [60].

2.5. Smart insulin

In February 2018, there were published data that at the Australian Institute of Bioengineering and Nanotechnology at the University of Queensland, researcher Dr. Chung Xu proved the concept of “smart” insulin delivery on mice, which provides for the release of insulin with an increase in blood glucose level [61]. If the blood glucose level is in the normal range, insulin is not released.

A nano implant that has a size of match can eliminate the need for daily injections of insulin. This achievement is one of the most promising in the field of diabetes treatment, which puts not only Queensland, but also Australia at the forefront of studies of nanoparticles that will have applications in many areas of medicine.

Scientists from the University of North Carolina and North Carolina State are also developing “smart” artificial beta cells that can detect the need for insulin and secrete it automatically [62].

Researchers have created cells that can be implanted subcutaneously and replaced every few days. As the results of studies on mice have shown, one injection of such cells normalizes blood sugar levels and retains levels for five days, according to an article published in Nature Chemical Biology journal [63].

The research team of North Carolina believes that their smart beta cells can be injected painlessly through a one-time skin-patch. Currently, they are developing a patch and are planning a preclinical trial of this technology. In addition, they are also working on an intelligent patch that will work without cells to determine blood glucose level and dosing insulin as needed.

2.6. Non-invasive glucometers

GlucoWatchBiografer of the first generation was approved by the US Food and Drug Administration (FDA) in 2001. According to FDA approval information, the device was described as a wristwatch with the function of a glucose monitoring system that allowed measurements every 20 min in the interval of up to 12 h and was used to track glucose levels over time. The device also had a built-in alarm function that triggered when the patient's glycemia readings were too high or too low.

A randomized study conducted by researchers at the University College of London, revealed further shortcomings of the GlucoWatch device. Their results were published in Diabetic Medicine journal in May 2009. Although only 6% refused to wear the device, participants noted inaccurate testimony of GlucoWatch G2 Biographer. Another clinical study from the Stanford School of Medicine showed that GlucoWatch often triggered a false alarm signal, erroneously informing about high rates of glycemia. Of the 20 alarms, only 10, announced as the correct results [64].

Now GlucoWatch disappeared from the field of diabetes treatment, and its manufacturer stopped further development.

The 2M Engineering solution is a non-invasive glucose monitoring. Accurate and painless monitoring of glucose without skin damage, measurement for 10 min and continuous monitoring of glucose [65] are declared.

In two papers published in the Optical Society's (OSA) open-access journal Biomedical Optics Expressgroups of researchers from the Netherlands and Israel describe two new devices that use changing patterns of scattered light to monitor biometrics: one monitors glucose concentration and dehydration levels, and the other one monitors the pulse [66].

According to the authors, the glucose sensor is the first portable device that can measure the concentration of glucose directly, but not invasively.

Glucowise is a 100% non-invasive device that uses a unique sensor technology that allows you to monitor your blood glucose level. It will be presented together with App and Smart Cloud technology. Assumes unlimited number of tests. A compact design should ensure a high level of confidentiality. The analysis will take, according to the authors, no more than 10 s. GlucoWise is still in development and is not available for public testing [67].

Sano is another project to introduce a non-contact glucometer to the market. A completely painless procedure is promised. A proprietary biometric sensor is used, which is contained in a convenient and low-profile patch. The mobile application is designed to optimize glycemic control. Sano technology helps to learn how the choice of nutrition affects human metabolism when training in real time mode [68].

2.7. Open questions

Taking into account the complexity of the problem of medical industry digitalization, implementation of digital solutions in the medical industry requires a clear understanding of the basic principles of medical certification of the involved digital, hardware and intellectual resources; reliable mechanisms for preserving personal and medical data; compatibility of used programs; availability of standards for digital medicine and standards for medical care; effective and reliable payment systems and legal grounds for receiving money by providers of medical telecommunications services; compliance when inputting data into individual electronic documentation from both physicians and patients; language localization of the software product; integration with local EHR systems; the inclusion of sections on affordable mHealthsolutions in the curricula of educational institutions; a thorough analysis of BigData; numerous clinical research of mHealth solutions; inclusion of possibilities of digital medicine in the protocols of medical care.

Conflict of interest

The authors have no potential conflict of interest to disclose.

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