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From biobanking to personalized prevention of obesity, diabetes and metabolic syndrome

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The growing prevalence of metabolic disorders creates an increasing demand for novel approaches to their prevention and therapy. Novel genetic diagnostic technologies are developed every year, which makes it possible to identify people who are at the highest genetic risk of diabetes, non-alcoholic fatty liver disease, and metabolic syndrome. Early intervention strategies can be used to prevent metabolic disorders in this group of people. Genetic risk scores (GRSs) are a powerful tool to identify people with a high genetic risk. Millions of genetic variants are analyzed in genome-wide association studies in order to combine them into GRSs. It has become possible to store and process such huge amounts of data with the help of biobanks, where biological samples are stored according to international standards. Genetic studies include more and more people every year that increases the predictive power of GRSs. It has already been demonstrated that the use of GRSs makes future preventive measures more effective. In the near future, GRSs are likely to become part of clinical guidelines so that they can be widely used to identify people at high risk for metabolic syndrome and its components.

Keywords: metabolic disorders, diabetes, obesity, non-alcoholic fatty liver disease, genetic risk score, biobank, GWAS (genome-wide association study).

Relationships and Activities: none.

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Introduction

The prevalence of such metabolic diseases as type 2 diabetes (T2D) and obesity grows every year and has become a pandemic in recent decades. According to the World Health Organization, the prevalence of obesity tripled between 1975 and 2016 and currently stands at ~39% among adults >18 years of age [1]. More than 422 million people worldwide suffer from diabetes, while in 2019, more than 1,5 million deaths were directly caused by diabetes [2]. T2D and obesity can be identified separately, but in most cases obesity is the main risk factor for T2D. According to the Multi-Ethnic Study of Atherosclerosis (MESA) and National Health And Nutrition Examination Survey (NHANES) studies, up to 41% of new T2D cases are caused by obesity, which indicates a close etiological and pathogenetic relationship of these diseases [3]. A set of metabolic disorders, including insulin resistance, obesity, increased blood triglycerides, decreased high-density lipoprotein cholesterol, combined with elevated blood pressure, are combined into the concept of metabolic syndrome (MS) [4]. Metabolic disorders are a known factor in the development of cardiovascular diseases. In diabetes, the risk of cardiovascular disease increases by 2 times [5]. According to a meta-analysis involving more than 300 thousand people, obesity increases the risk of cardiovascular events by 81% [6].

For several decades, the contribution of genetics to developing metabolic diseases has been studied. The contribution of heritability to obesity, as characterized by body mass index (BMI) or waist-to-hip ratio (WHT), is 40-70% [7, 8] and 30-60% [9, 10], respectively. The heritability of T2D is estimated at 36-72% [11, 12]. Obesity and T2D are multifactorial diseases, however, a number of monogenic forms are currently known, the diagnosis of which has already been included in modern clinical guidelines.

The significant contribution of heredity to MS makes it necessary to identify individuals with a high genetic risk in order to prevent metabolic disorders as early as possible. Evidence of the effectiveness of this approach in relation to coronary artery disease is described. According to the study by Damask A, et al. (2020), the risk of major cardiovascular events is significantly associated with high genetic risk, estimated on the basis of a scale that includes >6 million gene variants (hazard ratio (HR), 1,59; 95% confidence interval (CI): 1,28-1,96) [13]. At the same time, in the

highest risk group, the greatest effect was observed from lipid-lowering therapy with a Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (HR, 0,61; 95% CI: 0,45-0,84).

Diagnosis of polygenic metabolic diseases requires large resources and costs. To search for genetic polymorphisms that contribute to the development of certain diseases, studies are carried out using a genome-wide association study (GWAS) [14]. A significant number of GWAS are based on the genetic data of patients contained in biobanks. Predominantly based on the GWAS results, genetic risk scores (GRSs) are developed, which include nucleotide sequence variants (SVs), which together contribute the greatest risk of pathology. Similar studies are being conducted in relation to MS, T2D, obesity, non-alcoholic fatty liver disease (NAFLD) and other pathologies, which are discussed below.

The aim of this review was to assess the role of genetic diagnostics in the prevention of MS and its components. Much attention in the review is paid to the effectiveness of GRSs for genetic risk stratification, as well as the role of biobanking in the creation and validation of GRSs.

Material and methods

We searched for publications in Russian and English using following databases: MEDLINE, PubMed, Scopus, Cochrane Library, PEDro, eLIBRARY and Google Scholar. The search was carried out by following keywords (in Russian and English): метаболические заболевания, сахарный диабет, ожирение, неалкогольная жировая болезнь печени, шкала генетического риска, биобанк, GWAS, metabolic disorders, diabetes mellitus, obesity, non-alcoholic fatty liver disease, genetic risk score, biobank. The search depth covers the entire period until October 2021.

Molecular genetic diagnosis of metabolic disorders in modern clinical guidelines

In the latest clinical guidelines for the diagnosis and treatment of T2D, obesity, NAFLD, more and more attention is paid to potential of genetic methods that can assess the genetic susceptibility to a particular pathology. At this stage, the recommendations are mainly focused on monogenic forms of the disease, however, the introduction of GRSs into routine clinical practice in the foreseeable future seems very likely [15].

Diabetes

Personalized approaches are discussed in most detail in the 2020 American Diabetes Association (ADA) guidelines [16]. The role of genetic testing is especially important in the diagnosis of monogenic diabetes forms, since until now, a significant part of these disorders has not been detected due to similarity of its clinical manifestations with T2D. At the same time, the management tactics for these pathologies often differ, which makes the correct diagnosis of fundamental importance. In Maturity Onset Diabetes of the Young (MODY)-2, oral antidiabetic therapy is ineffective, while in MODY-1 or MODY-3, even small doses of sulfonylureas provide complete control of the disease [17, 18].

Genetic testing is not recommended for all persons with clinical manifestations of diabetes as a screening method, since this method remains quite expensive to date. It is proposed to use it only after identifying patients with the highest probability of monogenic diabetes. These include all children in whom diabetes was diagnosed in the first 6 months of life, as well as children with its manifestations and detected islet autoantibodies [19]. In other cases, if monogenic diabetes is suspected, a special MODY calculator should be used and only then a genetic study should be prescribed [20].

Another application of genetic analysis regards the identification of genetic defects that lead to inaccurate glycated hemoglobin (HbA_{1c}) results. They can be caused by various alterations in hemoglobin structure [16].

In T2D, genetic methods are still not recommended as routine methods for risk stratification, but there are prerequisites for GRS development, which will allow early identification of individuals at high risk of T2D. The 2019 Endocrine Society guidelines for the diagnosis and treatment of diabetes detail the obstacles to the creation of universal scores that combine clinical and genetic data. It is mentioned that GRSs are important not only for stratifying the diabetes risk, but also for changing the lifestyle of patients and disease control [21]. The review below discusses the most significant works in this field.

NAFLD

The risk of NAFLD is increased in patients with T2D and MS. In most cases, NAFLD is the result of long-term persistent metabolic disorders, but genetic predisposition also plays a large role in its development. Several genes have been identified in which SVs are associated with a high risk of this pathology. The most common mutations are found in the *PNPLA3* and *TM6SF2* genes. In accordance with the 2016 European Association for the Study of the Liver — European Association for the Study of Diabetes — European Association for the Study of Obesity (EASL–EASD–EASO) clinical guidelines, genetic testing is recommended in patients with suspected genetic etiology of NAFLD [22]. Routine genetic testing is not recommended.

Obesity

The European practical and patient-centered guidelines for adult obesity management emphasize the importance of etiology identification, in particular, the establishment of genetic risk factors for obesity [23]. The genetic etiology of obesity is most likely if the disease developed in childhood or if other family members have it. Currently, many genetic variants have been identified that are responsible for monogenic morbid obesity, and an even greater number of SVs that increase the polygenic risk of obesity. For example, up to 6%

of obesity cases among children and adults are due to mutations in the *MC4R* gene [24].

GRSs of metabolic disorders and personalized prevention

The role of biobanking in GRS development

Over the past decades, more data on the genetic mechanisms of developing many common diseases have been obtained. For this, the creation of biobank network around the world played a significant role. A biobank is a place of organized storage of biological material and data that can currently or in the future be used in clinical trials [25]. For the reliability of future results, it is extremely important that the procedures for collecting, processing, transporting and storing biomaterials are carried out in strict accordance with international standards [26]. A biobank may contain samples from thousands or hundreds of thousands of patients. Based on these data, it is possible to plan genetic studies, the huge scale of which is incomparable with previously available information. One of the most famous biobanks, the UK Biobank, contains samples from 500 thousand patients enrolled between 2006 and 2010. Since then, patients have been continuously monitored, and the biobank data is constantly being supplemented [27].

In Russia, biobanking also actively develops. One of the biobanks that meet international biobanking standards is the biobank of the National Medical Research Center for Therapy and Preventive Medicine. As of August 2021, this biobank contains biosamples of more than 54 thousand people, and the collection of samples is continuously updated [28]. In the modern world, the development of personalized medicine and early genetic diagnosis of diseases is unthinkable without a network of biobanks on an all-Russian and even global scale. Information technology makes it possible to process ever larger volumes of data, which opens up opportunities for starting ever larger projects.

Due to the availability of paid access to most of the largest biobanks, there are examples of successful analysis of information from biobanks in different countries. The recent study by Sakaue S, et al. (2020) analyzed data from 675898 patients from the UK Biobank, BioBank Japan and FinnGen [29]. The impact of genetic predisposition to obesity on life expectancy was assessed using GRS. Interestingly, high GRS rates for obesity had a significant effect on life expectancy in individuals whose samples were stored in the UK Biobank and FinnGen (HR=1,07; 95% CI: 1,05-1,09 and 1,06; 95% CI: 1,04-1,08; $p=1,7\times10^{-11}$ and $1,5\times10^{-8}$, respectively), while for BioBank Japan samples, the effect was less significant (HR=1,01; 95% CI: 1,00-1,02; $p=9,5\times10^{-8}$). This may be due to the fact that individuals from the Japanese Biobank have an average BMI <4 kg/m^2. The data obtained clearly demonstrate the need to create national biobanks and compare the results for different ethnic populations.

Prerequisites for GRS introduction into clinical practice

Currently, genetic research methods become increasingly confident in international clinical guidelines due to large-scale studies that reveal the potential of genetic diagnostics in clinical practice. They show how genetic data can complement information about the risk of metabolic disorders and what other possibilities genetic diagnostics have. For example, the GRS for predicting the obesity risk published in 2019, consisting of 2,1 million SVs, is based on data from >300000 UK Biobank patients [30]. The use of this GRS made it possible to determine that the polygenic risk may be equivalent to the obesity risk in rare monogenic mutations. The 10% of individuals with the highest genetic risk according to this GRS were 25 times more likely to develop obesity than the 10% of individuals with the lowest predisposition to develop obesity. Determining genetic risk in early childhood has also been shown to be highly accurate in predicting the obesity at 18 years of age: when comparing infants with the highest and lowest genetic risk and the same birth weight, it turned out that at 18 years the difference in average body weight between these groups was 12 kg. In another study based on a sample from the UK Biobank, a GWAS was performed that generated a GRS of WHR adjusted for BMI (WHR-BMI) of SVs and found that heritability and variant effects were stronger in women than in men as follows: GRS explained 3,9% and 3% of WHR-BMI variability, respectively. In 5% of allele carriers with the greatest WHR-BMI-increasing effect, the probability that WHR would exceed the threshold values characteristic of MS was 1,62 times higher than in 5% of allele carriers with the lowest WHR-BMI-increasing effect [10]. The study by Liu W, et al. (2021), also based on data from the UK Biobank, demonstrated the efficacy of GRS in diabetes [31]. An analysis of genetic data from 274029 participants showed that careful selection of SVs allowed the development of risk scores that had significant predictive value (area under the curve (AUC)=0,795; 95% CI: 0,790-0,800). Genetic analysis identified 30%, 12%, and 7% of patients with 5, 6, and 7-fold increased risk of diabetes, respectively. Mahajan A, et al. (2018), based on GWAS, created a GRS from 136795 SVs, which was applied to a sample from the UK Biobank (n=441894). C-statistic was 66%. Individuals with scores in the top 2,5% of GRS distribution had a 3,4-fold and 9,4-fold increased risk of T2D compared with study participants with scores below the median and 2,5 percentile, respectively [32]. Using this GRS in the GWAS meta-analysis (n=1407282), individuals with the highest GRS (90-100% percentile) were shown to have the highest risk of T2D (odds ratio=5,21, 95% CI: 4,94-5,49) compared with the control group (0-10% percentile) [33].

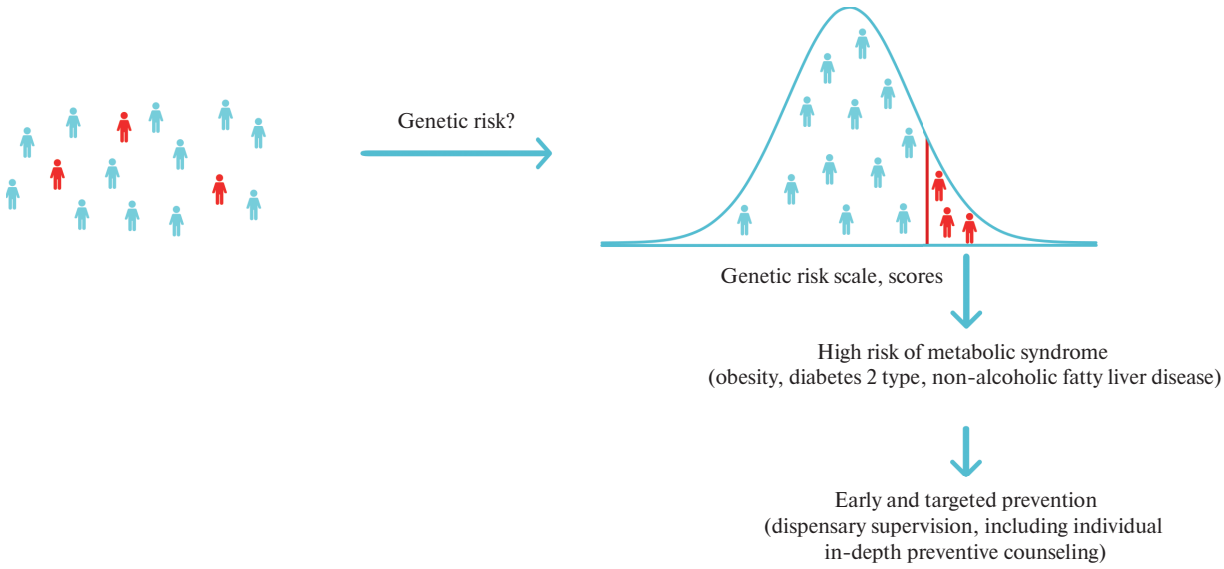

Figure 1. Algorithm of preventive interventions based on assessing the polygenic risk for MS and its components.

In another study, a metaGRS was developed from 1692 SVs, including 17 GRSs for phenotypes associated with T2D-2 and risk factors for atherosclerosis (T2D, HbA_{1c}, blood glucose levels 2 hours after a meal, fasting glucose and insulin, total cholesterol, high- and low-density lipoproteins, triglycerides, systolic and diastolic blood pressure, waist and hip circumference, BMI, height, smoking) [34]. GRS was learned on a UK Biobank sample of 47981 people and validated on 303053 participants (HR for T2D =1,32 (95% CI: 1,29-1,35) per metaGRS standard deviation). The addition of metaGRS to all common risk factors (RFs) significantly increased AUC from 0,850 (95% CI: 0,843-0,856) to 0,854 (95% CI: 0,848-0,860) ($p<0,001$). The addition of metaGRS to all standard RFs significantly increased the net reclassification improvement by 11,8% (95% CI: 9,2-14,2%). According to the study results, an approach that combines several GRSs into one metaGRS improves its predictive ability [34]. Often in clinical studies, the effectiveness of risk stratification using GRS and traditional risk factors is compared. A recent study analyzed the accuracy of T2D risk assessment using GRS and determination of BMI and birth weight [35]. Data were analyzed from 172239 adults who were able to report their birth weight to specialists and 287203 adults who reported their weight at age 10. The combined risk assessment included BMI at birth, age, and genetic risk. It turned out that with a combined use of genetic data and traditional risk factors, the assessment of T2D risk was the most accurate. The odds ratios in the 99^{th} percentile using single GRS, single BMI, and the combined estimate were 3,99, 7,84, and 9,38 for men and 3,94, 9,1, and 10,27 for women, respectively. These data indicate that the use of a combined risk assessment allows the most effective identification of patients with a very high predisposition to T2D. The authors note that a similar approach should be tested in risk stratification of other common diseases.

GRSs are a promising tool for developing personalized approaches to patient management. They allow not only to predict the risk of a particular pathology, but also to determine how effective preventive measures will be in different people. In a large study based on data from 276096 patients from the UK Biobank, the GRS of 2996760 SVs associated with T2D risk was used to monitor the effectiveness of lifestyle changes in various patient groups [36]. It turned out that in 1% of patients with the highest diabetes risk, lifestyle changes were accompanied by a reduction in absolute risk by 12,4% (95% CI: 10,0-14,9%), while in patients with the lowest genetic risk, preventive measures resulted in a risk reduction of only 2,8% (95% CI: 2,3-3,3%).

The study by Hardy D, et al. (2021), using a GRs of 16495 SVs, assessed how different dietary patterns (Western, healthy, and high-fat dairy) affect the MS likelihood depending on individual predisposition [37]. The analysis included 10681 patients from the earlier Atherosclerosis Risk In Communities (ARIC) study [38]. It turned out that the milk diet has the greatest protective properties against MS, while the protective effect is most pronounced in the lower GRS tertile (relative risk=0,47; 95% CI: 0,33-0,66; $p\leqslant0,001$). The risk of MS in the Western diet group was the highest regardless of genetic predisposition (relative risk was 1,52, 1,7 and 1,67 for 1, 2 and 3 tertiles of GRS, respectively).

With the help of GRS, it is possible to evaluate not only the effectiveness of preventive intervention, but also the potential effect of drug therapy. Li JH, et al. (2021) showed that patients with a higher genetic risk of T2D have a better response to sulfonylurea therapy than those with a low genetic risk [39]. Among

2228 patients with a mean age of 59,7 years, the mean genetic risk for T2D was 74,92 with the range from 53,29 to 93,08). With a one standard deviation increase in risk with sulfonylurea therapy, there was an additional decrease in HbA_{1c} levels of 0,063% (p=0,02).

The results of presented studies demonstrate the need for early and targeted preventive interventions in identifying individuals with a high predisposition to MS or its components. GRS is currently used only for research. However, GRS introduction into clinical practice can significantly contribute to personalized prevention of metabolic diseases. When assessing the polygenic MS risk at the population level, it will be possible to identify a group of people who need its early and targeted prevention (Figure 1). Polygenic risk assessment should be carried out at a young age, preferably even before exposure to traditional RFs [15]. In accordance with the current regulatory documents on medical screening, persons with a high polygenic risk of MS can potentially be assigned to health group II and need dispensary follow-up by a general practitioner with individual in-depth preventive counseling [40]. Preventive counseling should be expanded on the prevention of obesity, carbohydrate and lipid metabolism disorders. In this group, the examination expansion should be considered to identify existing metabolic disorders, in particular, the lipid profile assessment, and not just the level of total cholesterol. An important aspect of prevention in those with a polygenic MS risk is competent information about the genetic predisposition to the disease, aimed at encouraging the patient to improve their lifestyle.

Conclusion

In recent decades, there is a significant acceleration in genetic testing introduction into clinical practice. Many clinical guidelines emphasize the need for genetic testing in cases of suspected monogenic forms of obesity, T2D, and NAFLD. GRSs are increasingly being used. There are prerequisites for the creation of scores that have additional prognostic value compared to traditional risk factors for metabolic diseases. Moreover, there is evidence of an increase in prevention effectiveness in high polygenic risk groups due to GRS use. In the future, polygenic risk assessment of MS and its components is expected to be introduced into routine practice, which is facilitated by the development of a biobank network around the world and the accumulation of large arrays of genetic data. Increasingly large-scale genetic studies provide more information about the hereditary predisposition to MS, which allows the development and improvement of personalized approaches to its prevention.

Relationships and Activities: note.

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