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Значение результатов полногеномных исследований для первичной профилактики сахарного диабета 2 типа и его осложнений. Персонализированный подход

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Метод исследований общегеномных ассоциаций (Genome-Wide Association Studies – GWAS) уверенно становится основой для поиска генов-кандидатов моногенных и мультифакторных заболеваний, включая сахарный диабет 1 и 2 типа, ишемическую болезнь сердца, ожирение, заболевания сосудов и другие. К настоящему времени открыто более 40 локусов, ассоциированных с сахарным диабетом 2 типа (СД2), установлены генетические факторы предрасположенности в отношении сердечно-сосудистых заболеваний. Результаты GWAS позволяют в ряде случаев не только понять патофизиологические основы заболеваний, но и могут служить толчком для создания новых лекарственных препаратов. Вместе с тем, закономерно возникает вопрос о возможности применения накопленных знаний для прогнозирования развития заболеваний, в том числе СД2 и его сосудистых осложнений. В обзоре представлены литературные данные о возможностях использования результатов GWAS для расчета риска развития СД и сердечно-сосудистых заболеваний. Определение индивидуального генетического риска позволит проводить первичную профилактику заболеваний и в ближайшее время, по всей видимости, будет являться основой персонализированной предиктивной медицины.
Ключевые слова: *сахарный диабет; сердечно-сосудистые заболевания; исследования общегеномных ассоциаций; риск развития, прогнозирование*

Significance of the results of genome-wide association studies for primary prevention of type 2 diabetes mellitus and its complications. Personalised approach.

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The method of Genome-Wide Association Studies (GWAS) steadily becomes the basis for searching for candidate genes of monogenic and multifactorial diseases, including type 1 and 2 diabetes mellitus, coronary heart disease, obesity, vascular diseases, and others. To date, approximately 40 loci associated with type 2 diabetes mellitus (T2DM) have been identified and genetic predisposition factors for cardiovascular diseases have been determined. In some cases, the GWAS results not only enable understanding of the pathophysiologic basis for diseases, but also may give rise to new drugs. However, the question naturally arises about the possibility of implementing the accumulated knowledge to predict the development of diseases, including T2DM and its vascular complications. This review summarises the literature data on the possibilities to use the GWAS results to calculate the risk of developing diabetes and cardiovascular diseases. Determination of the individual genetic risk will allow for the primary prevention of diseases and will apparently be the basis of personalised predictive medicine in the near future.
Keywords: *diabetes mellitus; cardiovascular diseases; genome-wide association studies; risk of development; prediction*

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The concept of 'P4 medicine' was declared as one of the new trends in the health development in Russia [1]. Professor Leroy Hood, President and Co-Founder of the Institute for Systems Biology (USA), suggested the basic principles and the name of the new trend in healthcare, P4 medicine, which is based on 4 basic principles as follows:

- predictiveness - allows one to predict diseases on the basis of the individual features of the genome (creation of probabilistic health prognosis on the basis of genetic studies);
- prevention (Fr. *préventif*, from Lat. *praevenio* - advance, prevent) - means to work proactively and to preclude the development of diseases through their prevention;
- personalisation - based on an individual approach to each patient, which, among other things, suggests the creation of a unique genetic passport for the treatment and control of the patient's health and
- participation (partnership) - based on a broad collaboration of various medical professionals and patients as well as on the transformation of the patient from the subject of treatment to the object of the treatment process.

This approach is largely associated with 2 major scientific and technological achievements: implementation of the 'Human Genome' project and creation of technical solutions for the active use of genome-wide association studies (GWASs). The book 'Genetic Passport: the Basis of Individual and Predictive Medicine', edited by Dr. Med. Sci., Professor V.S. Baranov, Corresponding Member of the Russian Academy of Medical Sciences, was published in 2009 [2]. In this book, the authors make it clear that the fundamentals of preventive personalised medicine are based on the knowledge of individual features of the genome structure, deciphering which has become possible in recent decades.

Currently, the problems of preventing diabetes mellitus (DM) and its complications rank among the major medical and social tasks worldwide.

The number of DM patients increases every year and has reached epidemic proportions. The modern basis for prevention of DM is built on identifying the risk factors for DM and implementing appropriate interventions. For example, the main risk factors for type 2 diabetes mellitus (T2DM) are [3] as follows: age of >45 years; overweight and obesity (particularly the visceral type); decreased physical activity; presence of DM in relatives; ethnic features; history of gestational DM (or birth weight of >4,500 g) and presence of conditions such as impaired fasting glycaemia or impaired glucose tolerance, arterial hypertension, dyslipidemia (HDL cholesterol levels of ≤0.9 mmol/L and/or triglyceride levels of ≥2.82 mmol/L), polycystic ovary syndrome and cardiovascular diseases (CVDs). Overweight and obesity are the major risk factors for the development of T2DM. Therefore, diagnosis of dysfunctional carbohydrate metabolism is indicated for all individuals with a body mass index (BMI) of ≥25 kg/m2 if they have at least one of the factors mentioned above.

Conditions such as impaired fasting glycaemia or impaired glucose tolerance, impaired glucose metabolism during pregnancy, obesity and dyslipidemia are already separate pathological processes requiring treatment. Like most multifactorial diseases, the risk of developing T2DM is influenced by genetic and environmental factors. The rapid pace of urbanisation, prevalence of a sedentary lifestyle and alterations in the diet are largely responsible for the growing epidemic of obesity and subsequently, T2DM [4]. There is no doubt regarding the contribution of genetic factors to the development of the disease, as indicated by a high level of concordance in monozygotic twins of T2DM and familial inheritance. However, the problems of studying the genetic basis of T2DM are associated with the polygenic nature of the disease. When a variety of genes are involved in the development of a pathology, the processes regulated by these genes are closely interconnected. The presence of epistatic interactions can alter the contribution of candidate genes to the genesis of the disease under various external influences. Further, the genetic features of T2DM include unstable penetrance (10%–40%) and a high frequency of alleles with a weak or moderate effect on the predisposition to the disease (odds ratio of 1.1–1.5) [5]. A significant breakthrough in the study of the genetic predisposition to T2DM and its complications was made through whole-genome studies and active implementation of GWASs.

Contribution of the results of GWASs to the genetics of T2DM

Modern technologies developed by Illumina, Affymetrix and other companies allow one to create so-called high-resolution arrays that include 300,000–2,000,000 single nucleotide polymorphisms (SNPs) for an individual DNA. An SNP is a single nucleotide substitution in a specific DNA sequence. Theoretically, an SNP is observed at a frequency of 1 per 100–300 nucleotides. At this frequency, an SNP best meets all the requirements that are applicable to markers for large-scale studies of linkage. In some cases, an SNP may represent a mutation that causes a hereditary disease [6]. Several million SNPs have been identified and confirmed by the International HapMap Project. Initially, 270 individuals from 4 populations were genotyped by the HapMap project. The project created the SNP haplotype map that comprises information about the distribution and frequencies of marker SNPs in the studied populations. Moreover, 1000 genome projects have been completed performed, which greatly increases the amount of information, and more than 5 million SNPs are considered in the present GWAS [7].

Comparison of the corresponding allele frequencies in patients and healthy individuals allows identification of all SNPs, genes and genomic loci associated with a particular disease, allowing the determination of the specific genetic

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profile of a multifactorial disease. The higher frequency of a specific SNP in a disease group compared with controls suggests its association with the disease. These studies are conducted according to the case-control principle and include analyses of thousands of observations.

A GWAS does not require a hypothesis explaining the origin or mechanism of a disease or trait; it identifies a correlation between a phenotype and a genetic marker or a set of markers. In contrast to GWASs, classical studies on the association of candidate genes with a disease are based on the assumption that the gene under study should be associated with the pathology, i.e. they require an initial hypothesis. One of the obvious advantages of GWASs is that the results on the association of certain SNPs with a disease allow making an assumption about the contribution of the relevant genes to pathogenesis. Thus, the question of mechanisms that influence each gene and their contribution to the pathology forms the next challenge. GWAS technology is arguably the basic method for searching for candidate genes of monogenic and multifactorial diseases, including type 1 diabetes mellitus (T1DM), T2DM, coronary heart disease (CHD), obesity and vascular diseases.

The first GWAS of T2DM was conducted in France and included 661 patients and 614 control subjects. The study associated numerous SNPs to T2DM, including *SLC30A8, HHEX, LOC387761* and *EXT2* and confirmed the previously established association of DM with *TCF7L2* [8]. A short time later, the association of *SLC30A8* and *HHEX* with T2DM was confirmed and *CDKAL1* was identified as well [9]. In 2007, a collaborative study conducted by the Wellcome Trust Case Control Consortium/United Kingdom Type 2 Diabetes Genetics Consortium (WTCCC/UKT2D), the Finland–United States Investigation of NIDDM (FUSION) and the Diabetes Genetics Initiative (DGI) published data confirming the relationship of SCL30A8 and HHEX with T2DM and established the association of the new genes *CDKAL1, IGF2BP2* and *CDKN2A/B*. The relationship of the latter genetic loci and variants of *PPARGP12A, KCNJ11* and *E23K* with T2DM was confirmed by numerous studies in European and non-European populations. The WTCCC/UKT2D study established the relationship between certain variants of *FTO* and T2DM; however, further studies demonstrated that this effect was largely attributable to an increase in body weight.

Other studies attempted to increase the sample size to identify new genetic loci with a reduced predisposition to the disease. The 3 organisations mentioned above combined their data to form a single Diabetes Genetics Replication and Meta-analysis (DIAGRAM) consortium. Five new loci, including *JAZF1, CDC123/CAMK1D, TSPAN/LGR5, THADA* and *ADAMSTS9,* were identified by analysis of 4,549 patients with T2DM and 5,579 control subjects (2.2 million SNPs) [10]. At present, the association of large cohorts of patients with T2DM is the subject of similar studies that have analysed more than 22,000 individuals in Europe. In recent studies, 2,426,886 autosomal SNPs as well as SNPs located on the X-chromosome were analysed, and 12 more loci demonstrated a significant association with T2DM ($P < 5 \times 10^{-8}$) [11]. To date, approximately 40 loci associated with predisposition to T2DM have been identified, with most being discovered using GWASs.

The role of many of these genes in disease pathogenesis is known. In particular, *TCF7L2* and *HHEX* encode transcription factors that regulate the activity of other genes [12]. Animal studies demonstrate that the absence of these genes inhibits pancreatic activity. For example, EXT2 plays a role in the embryonic development of the embryo and in many organs, including the pancreas. *SLC30A8* encodes the ZnT8 protein that participates in zinc transfer, which, in turn, allows storage of insulin in pancreatic β-cells [13]. The results of the Helsinki Birth Cohort Study suggest an association of *HHEX-IDE, CDKN2A/2B* and *JAZF1* with a low birth weight [14], which is associated with the development of T2DM.

GWAS results not only increase our understanding of the pathogenesis of T2DM but may also facilitate the development of new drugs. For example, *TCF7L2* variants are associated with clinical effects induced by the administration of glucagon-like peptide-1 analogues [15], and *OCT1* variants are associated with clinical effects induced by metformin therapy [16].The polymorphic marker rs11212617, located adjacent to a mutant ataxia telangiectasia (ATM) gene, is also associated with the clinical effects of metformin [17]. *PPARG* and *KCNJ11,* which are candidate genes for the predisposition to T2DM, are associated with substances that are targets for antidiabetic drugs (thiazolidinediones and sulfonylurea derivatives) [18, 19]. However, the data regarding the relationship of certain polymorphic markers with the metabolism of metformin and other hypoglycaemic agents are currently uncertain and may not be applicable for determining an individual's response to the action of hypoglycaemic agents.

One of the disadvantages of SNP analysis is that the subsequent identification of the causative variant within the associated locus may be an arduous task. For example, *IL2RA* is adjacent to *IL15R*, which is another possible candidate gene associated with T1DM. Therefore, it is possible that a particular locus may be associated with a disease not because it is causative but because both loci are in linkage imbalance [20].

Possibilities of using GWAS results to predict the development of T2DM

Undoubtedly, the question arises about the possibility of using the results of GWASs to calculate the risk of developing T2DM and to prevent it. The results of the Diabetes Prevention Program (DPP) study [21] are an example. People with the TT allelic variant of the polymorphic marker rs7903146 within TCF7L2 had a significantly higher risk of transitioning from the impaired glucose tolerance stage to DM compared with carriers of the

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CC allelic variant [hazard ratio (HR), 1.55; 95% CI, 1.20–2.01, P < 0.001). Moreover, the genotype effect was more pronounced in the placebo group compared with groups with a modified lifestyle or treated with metformin. The TT genotype was associated with reduced insulin secretion but not with measures of insulin resistance. Similar results were obtained for the marker rs12255372 within *TCF7L2*.

The importance of studying an individual's genetic predisposition to T2DM is indicated by the results of 2 large complementary studies. The first study demonstrated the dependence of the risk of developing T2DM on fasting glucose levels [22]. From 1 January 1997 to 31 November 2000, the cohort of 46,578 people had fasting plasma glucose (FPG) levels of <100 mg/dL (5.55 mmol/L). This group was observed until 30 April 2007. All deaths and DM development were recorded. After completion of the survey, the subjects were divided into 4 categories depending on the initially determined levels of FPG: <85 mg/dL (4.7 mmol/L), 85–89 mg/dL (4.7–4.94 mmol/L), 90–94 mg/dL (5–5.2 mmol/L) and 95–99 mg/dL (5.3–5.5 mmol/L). There were 1,854 newly diagnosed patients with T2DM during the observation period. The mean time of disease development was 54.6 months from the start of the observation period. The risk of developing T2DM in these groups was calculated using Cox regression analysis considering age, gender, BMI, arterial pressure (AP), blood lipid levels, smoking, cardiovascular pathology and hypertension. Regardless of these risk factors, the FPG level was observed to be an independent risk factor for developing T2DM, and each higher increment of FPG level increased the risk by 6% (HR, 1.06; 95% CI, 1.05–1.07, P < 0.0001). For patients with FPG levels of <85 mg/dL (4.7 mmol/L), the risk was determined to be 3.1/1000 (95% CI, 2.6–3.1) and the risk for patients with FPG levels ranging from 95 to 99 mg/mL (5.3–5.5 mmol/L) was 9.9/1000 (95% CI, 9.3–10.0). Thus, it was observed that the relative risk increases by a factor of approximately 3 and occurs within the normal range of FPG levels.

The second large study [23] evaluated the effect of individual genotype on fasting glucose levels of healthy children and adolescents. There was a statistically significant association of polymorphisms of *ADCY5 (rs11708067), CRY2 (rs11605924), GLIS3 (rs7034200), PROX1 (rs340874), SLC2A2 (rs1920090), G6PC2 (rs560887), MTNR1B (rs10830963), SLC30A8 (rs1326624)* and *GCK (rs4607517)* with fasting glucose levels and 16 SNPs were identified. The difference in the FPG values was 0.25 mmol/L (95% CI, 0.15–0.35) upon comparison of children and adolescents with low and high genetic risks. Weighted risk analysis revealed an increase in fasting glucose levels by 0.026 mmol/L (0.021–0.031) for each dominant negative allele. With this exception, the effect of these markers on fasting glucose levels does not depend on age. A meta-analysis of 6 studies conducted in Europe, including a total of 6,000 boys and girls aged 9–16 years, showed that the new loci associated with FPG levels in adults identified using GWASs are also associated with FPG levels in healthy children and adolescents. Taking into account the results of the above study, which demonstrates the relationship between the risk of developing DM and FPG levels, the effect of these loci on the risk of developing T2DM becomes obvious. Children and adolescents with alleles of *G6PC2, MTNR1B, GCK* and *GLIS3* associated with increased FPG levels also showed deterioration of the β-cell function as assessed by the HOMA model.

Studies on the possibility of predicting the risk of T2DM according to the calculation of the genetic risk have been conducted for nearly 10 years. Some such as the Framingham Offspring Study, the Malmö Preventive Project and the Botnia Study [24, 25] have not demonstrated the advantage of predicting the disease risk with allowance for the genetic risk. In this case, analysis involved 11–20 loci associated with T2DM. However, the authors suggested that calculating the genetic risk of developing the disease and genetic testing may be more useful in young people before they develop phenotypic traits, which are risk factors for T2DM. For example, re-analysis of 40 loci identified by the Framingham Offspring Study by de Miguel-Yanes et al. [26] demonstrates that the genetic risk of developing DM is higher for people aged <50 years.

Most studies, which usually analyse thousands of participants, determine the association of SNPs with available and commonly used parameters of the β-cell function and insulin resistance, primarily according to the results of the oral glucose tolerance test (OGTT). Tests include determining fasting glucose and insulin levels at 30 min, the Matsuda index and the area under the insulin secretion curve. However, it should be noted that the indices obtained from OGTT do not provide information regarding the mechanisms of impaired glucose uptake, the impaired secretion of glucagon and a possible effect of incretins on postprandial glycaemia. This may explain, at least in part, why most of the loci associated with T2DM according to GWAS results are associated with impaired secretion of insulin but not with its action [27–29].

Strategy for preventing CVDs based on the calculation of the total cardiovascular risk (CVR)

An independent problem of DM is the development of vascular complications or progression of existing CVDs such as CHD, myocardial infarction, peripheral vascular diseases and arterial hypertension. These diseases often cause disability and mortality. The European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2012) [30] are as follows:

- CVDs affect males and females; of all deaths in Europe that occurred before the age of 75 years, 42% in females and 38% in males were caused by CVDs;
- CVD mortality is changing; age-standardised rates declined in most European countries but remain high in Eastern Europe;

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- prevention is effective; reduced mortality from CHD was associated with the impact on the risk factors in 50% cases and with improved treatment in 40% cases;
- preventive efforts should be lifelong and
- population and high-risk preventive strategies should be complementary; an approach limited to high-risk persons will be less effective and population education programmes are required.

One of the main tools for the prediction and primary prevention of CVD is calculating the total CVR. The present CVD risk assessment systems were developed for patients with DM and the general population. However, there are much fewer patients with DM. The Russian national guidelines on CVD treatment suggest that, in general, a patient's individual CVR should be evaluated, and treatment covered by medical insurance will be administered to patients with a high CVD risk [31, 32]. Calculating CVD risk will likely continue to aid setting treatment priorities.

CVD risk assessment systems were developed on the basis of analysis of large population-based studies, including 15 in the USA and Europe and 2 in China. The cohort ranged from 1,500 to 205,178 people who were studied for 4.7–25 years. Eight studies were conducted in patients with T2DM and 9 in the general population. Most risk assessment systems included standard factors such as age, gender, smoking, AP and cholesterol levels [33].

Several models to assess total CVR were developed according to the data acquired from prospective studies. The Framingham scale was the first to employ a model of total CVR derived from the Framingham Heart Study (1949–1984). The risk factors for CHD, stroke, sudden death and heart failure were determined. The risk scale predicts these events during the next 10 years for males and females. Five factors [2 non-modifiable (gender and age) and 3 modifiable (smoking, systolic blood pressure and total cholesterol levels)] were incorporated into the calculation of the risk. More accurate data for assessing the total risk were provided by the mathematical Prospective Cardiovascular M nster (PROCAM) model in the form of the Coronary Events Risk Calculator (CERCA) software developed according to the results of a prospective study [34]. This model estimates the risk of developing CHD complications, specifically myocardial infarction and sudden death in males and postmenopausal females in the next 8 years. Nine risk factors were previously identified as follows: 3 non-modifiable (age, history of myocardial infarction and hereditary burden) and 6 modifiable [smoking, systolic AP, total cholesterol levels, low HDL levels and DM)].

The European Society of Cardiology developed the European Systematic Coronary Risk Evaluation (SCORE) model [30] on the basis of the data from prospective studies conducted in 12 countries in Europe, including Russia, which involved 205,000 patients and lasted 27 years. In contrast to the Framingham study, which evaluated the 10-year risk of developing fatal and non-fatal coronary events, the European SCORE model specifically assesses the 10-year risk of all fatal events associated with atherosclerosis and arterial hypertension, including myocardial infarction, stroke and peripheral artery diseases. Calculations of the total risk employed the factors of the Framingham study. According to the SCORE model, individuals at a very high risk of a fatal event include the following:

- those diagnosed with CVD with previous myocardial infarction and acute coronary syndrome who underwent vascular surgery and other revascularisation manipulations;
- those with DM (types 1 and 2) with one or more cardiovascular risk factors and/or damage to target organs (microalbuminuria, 30–300 mg/day);
- those with severe chronic kidney disease (CKD) (glomerular filtration rate of <30 ml/min/1.73 m^2) and
- those for whom the 10-year risk of fatal events calculated according to SCORE is ≥10%.

Patients with T1DM or T2DM without CVD risk factors or damage to target organs have a high 10-year risk of fatal events (≥5% and <10%, respectively).

Population-based studies [35, 36] identified additional CVD risk factors for patients with DM as follows: age at diagnosis, DM duration and DM compensation parameters (glycated haemoglobin and fasting glycaemia levels). However, the search continues for models to predict CVR in patients with T2DM. For example, a model to assess the 4-year CVD risk was proposed in the Action in Diabetes and Vascular Disease Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study. The study selected 7,168 subjects without previous CVD [30] and detected 473 major cardiovascular events. The study identified age at diagnosis, duration of DM, gender, blood pressure, pulse, treatment of hypertension, atrial fibrillation, retinopathy, HbA_{1c} levels, albumin/creatinine ratio in urine and initial HDL cholesterol levels as significant predictors of cardiovascular events.

These CVD risk assessment studies mainly focused on fatal cardiovascular events during the next 8–10 years. In this case, the risk factors, which are assumed to be affected, are now chronic progressive severe diseases such as arterial hypertension, DM and dyslipidemia. Therefore, it is difficult to assess early primary prevention of arterial hypertension, CHD and atherosclerosis at other sites. Thus, it is important to predict preclinical CVD and recognise that all risk prediction systems are not ideal and that they must be applied by qualified specialists.

Total risk is not a comprehensive concept, because the significance of individual risk factors is ambiguous. For example, examination of 87,869 males diagnosed with coronary artery disease revealed that 19.4% had none of the 4 major risk factors (hypertension, smoking, hypercholesterolemia and DM), 43% had 1 factor, 27.8% had 2 factors, 8.9% had 3 factors and only 0.9% had all 4 [38]. Further, the significance of each individual risk factor in the development of CVD and the requirement for specific

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therapeutic measures are not always clear. For example, blood lipid levels are an insignificant factor for females in the low risk group, according to the calculation of the risk of fatal CVD using the SCORE scale (Table 1). Moreover, the risk of fatal CVD in females with cholesterol levels of 8 mmol/L, normal blood pressure and without smoking may be lower by a factor of 10 compared with that in a smoking male of the same age with arterial hypertension but with cholesterol levels of <5 mmol/L.

Taken together, these findings suggest that new biochemical and genetic markers are required to determine the risk of CVD. Interest in the latter is driven by the possibility of using results acquired from younger subjects before the development of the early stages of the disease, i.e. to conduct primary prevention of CVD for people with DM as well upon detection of impaired glucose tolerance or fasting glycaemia.

Assessment of individual genetic risk of CVDs is the basis of personalised predictive therapy

The genetic factors of predisposition to the above-mentioned diseases, which to a great extent determine their development, have already been established (Table 2). Within the framework of the WTCCC project that examined 1,988 patients with CVD and 5,380 healthy subjects, 18 SNPs significantly associated with an increase in the relative risk of developing CVD were identified [39]. Values of the relative risk for each polymorphic marker ranged from 1.12 to 1.47. Nine SNPs were associated with lipid metabolism, and 9 represented independent risk factors for CVD, in particular *MIA3, WDR12, MRAS, PHACTR1, MTHFD1L, CDKN2A/2B, CXCL12, SMAD3* and *SLC5A3 (MRPS6)*. A linear relationship between the number of risk alleles and the risk of developing CVD was established. For example, every negative allele increased the relative risk of developing CVD by a factor of 1.18 (95% CI, 1.15–1.22). The total (cumulative) CVD risk for the analysed alleles was 2.21 (95% CI, 1.87–2.61). Allowing for the average incidence of CVD in a population, an increase in the probability of its development by a factor of 2.21 supports the assumption that the disease will develop in people with these genotypes.

How does the genetic nature of CVD risk correlate with the level of risk calculated according to clinical signs? To answer this question, a study was conducted in 1,243 people without CVD [40]. Assessment of CHD risk (myocardial infarction and sudden cardiac death) was performed according to the Framingham risk scale and genetic scale. GWAS data for 11 SNPs associated with CHD were used to calculate the latter. Assessment of the risk calculated after adding the data of the individual genetic risk led to a significant reclassification of the 10-year CHD risk and was not consistent with the data calculated according to the Framingham risk scale alone. This study did not allow

Table 1

Combinations of risk factors for developing fatal CVDs for 10 years according to SCORE [30]

Gender	Age, years	Cholesterol, mmol\L	Systolic AP, mmHg	Smoking	Risk, %
Females	60	8	120	No	2
Females	60	7	140	Yes	5
Males	60	6	160	No	8
Males	60	5	180	Yes	21

quantitative assessment of the accuracy of reclassifying the degree of risk with allowance for the contribution of the genetic risk. Further studies are required to determine whether identification of predisposing SNPs helps improve the accuracy of cardiovascular risk stratification and whether a comprehensive genetic risk for common diseases has clinical application.

It should be emphasised that the risk factors are lifelong. However, their manifestation is observed at different ages and to different extents and depends not only on the genotype but also on environmental factors, diet and lifestyle. This suggests the requirement for prevention and rehabilitation programmes to address lifelong genetic predisposition according to age and changes in health.

Similar to other multifactorial diseases, genetic factors that determine an individual's predisposition to T2DM are linked to specific conditions and triggers. However, under the same lifestyle conditions, individuals with the highest genetic predisposition and higher genetic risk for the disease are more likely to develop T2DM. The Health Professionals' Follow-up Study [41], which included 1,196 males with T2DM and 1,337 healthy males, identified a significant relationship among the so-called 'Western' dietary pattern, individual genetic risk and risk of developing T2DM (Fig. 1). The individual genetic risk was calculated according to the analysis of 10 SNPs associated with T2DM. Diet was assessed using a questionnaire covering qualitative and quantitative characterisation of 40 food groups. Multivariate analysis identified 2 major dietary patterns, 'Western' and 'Healthy'. The 'Western' pattern was characterised by consumption of foods such as processed meats, red meat, high-fat butter, dairy products, eggs and processed grains. The 'Healthy' diet was characterised by consumption of large amounts of vegetables, fruits, legumes, whole-grain products, fish and poultry. Despite the dietary pattern, the risk of developing T2DM was determined by the genetic risk of developing DM. For example, in males with a high genetic risk of developing DM (>12 alleles associated with increased DM risk) associated with the 'Western' dietary pattern, the risk of developing DM ranged from 1.23 (95% CI, 0.88–1.73) to 2.06 (95% CI, 1.48–2.88) depending on the dietary pattern as well as age, BMI, smoking, alcohol consumption, physical activity and DM in relatives. However, among males with a lower genetic risk, adherence to the 'Western' dietary pattern was not significantly associated with the risk of developing

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Table 2

Genetic markers for CVDs and obesity	
Nosology	Genes
CHD	*HNF1A, MRAS, MTHFD1L, CDH13, SEZ6L, SMAD3, Intergenicrs 501120, rs3008621, rs1333049, rs2943634, rs383830, rs17411031*
Myocardial infarction	*CXCL12, MIA3, PCSK9, PHACTR1, SH2B3, WDR12,OR13G1, PRR4, Intergenicrs 646776, rs9982601, rs10757278*
Obesity	*FTO, MC4R, INSIG2, PCSK1*
Peripheral artery diseases	*CHRNA3*
Arterial hypertension	*BCAT1, PRARGCIA*

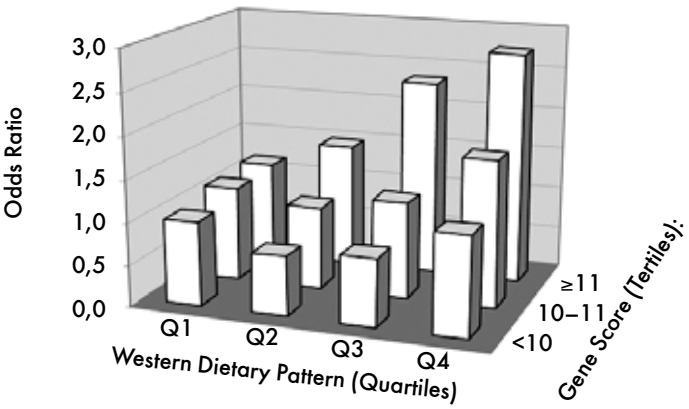

Fig. 1. Risk of developing DM (odds ratio) depending on the diet (Quartiles) and genetic risk (<10, 10–11 and ≥12) [41].

DM. Further, it was observed that consumption of red meat and meat products, in particular, increases the risk of DM to the maximum extent in males with a high genetic risk (>12 high-risk alleles) but does not affect the disease risk in individuals with a lower genetic risk (Fig. 1).

Although there is little evidence to indicate that providing genetic information may lead to changes in a patient's lifestyle and attitude towards health, it is possible that implementation of affordable genetic testing and detection of genetic predisposition will serve as powerful motivators and will focus the physician's and patient's attention on the prevention of an underlying disease and its complications [42].

CONCLUSION

High-throughput nucleotide sequencing techniques make it possible to determine an individual's complete genome sequence. Further studies should be aimed at understanding this wealth of information to determine the association of genotype with clinical signs. In particular, genetic information should be collected from individuals with a disease or certain conditions. Despite the enormous collection of relevant data, further understanding and practical application are not possible without the cooperation of specialists (e.g. clinicians, biochemists and geneticists). For example, a meta-analysis published in 2010 analysed the relationship between genetic and biochemical factors and the development of ischemic stroke and CHD [43] to determine whether ischemic stroke and CHD share genetic determinants and the comparative significance of genetic and biochemical markers for predicting the risk of stroke. The analysis included 187 genetic studies involving 37,481 patients and 95,322 control subjects (43 polymorphisms of 29 genes were studied), 13 meta-analyses of the genetic determinants of CHD, 146 studies (65,703 participants) describing the interaction of genetic and biochemical factors and 28 studies (46,928 participants) reflecting the main biochemical risk factors for ischemic stroke. Most genetic studies revealed an association of the risk of ischemic stroke and CHD, although differences were identified for some genes. The association between 4 most frequently detected genes associated with stroke and biochemical predictors of this disease was established.

As the number of confirmed correlations between genetic markers and clinical features increases, analysis of an individual's genome will be more informative. The goals of preventive medicine should comprise the following:

- to develop a prevention programme for specific somatic diseases in individuals with a genetic predisposition to a particular disease;
- to predict the development of existing somatic diseases and to provide the most appropriate treatment according to the identified genetic factors and
- to predict the development of complications of somatic pathology on the basis of the calculation of genetic risks.

DISCLOSURE INFORMATION

The authors declare no duality (conflict) of interest relevant to this article.

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