PHARMACOGENETIC BIOMARKER FACTORY: HOW DOES IT WORK?

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ABSTRACT

Despite the strides made in the study of -omics data, including pharmacogenomic data, there is still a lack of reliable, reproducible, sensitive, specific and, most importantly, clinically useful biomarkers for predicting response to drug treatment in real clinical practice. An important impact in the development and implementation of new pharmacogenetic biomarkers can be made by the creation of an appropriate ecosystem around biomarkers by uniting capacities of academic and research centers, biomedical laboratories and pharmaceutical companies, IT and artificial intelligence companies into consortiums. The article provides an overview of the so-called "biomarker factory", which allows to build and systematize the process of introducing a pharmacogenomic biomarker into clinical practice.

Key words: biomarkers, consortiums, omics technologies, personalized medicine, pharmacogenetics, scientific groups.

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INTRODUCTION

Over the past decade, various strategies for the development of personalized medicine have been implemented and implemented at the state level in many developed countries, including the financing of large research projects for the development and implementation of new omics technologies in clinical practice. Examples of such programs are: Order of the Ministry of Health of Russia of February 1, 2019

42 (as amended on August 24, 2020) "On approval of the departmental target program "Development of Fundamental, Translational and Personalized Medicine", "The Concept of Predictive, preventive and personalized medicine in the Russian Federation until 2025" and the priority direction of scientific and technological development until 2035 -

"Transition to personalized medicine, high-tech healthcare and health saving technologies, including through the rational use of drugs (primarily antibacterial) in the Russian Federation, The Precision Medicine Initiative in the United States of America, The 100000 Genomes Project in the United Kingdom, National Strategy for Personalized Medicine in Denmark, "The MeDeA (Medicina Personalizada Aplicada, Applied Personalized Medicine)" in Spain, Horizon 2020 in the EU as a whole, and many others [1—6]. One of the most dynamically developing omics technologies of personalized medicine is genomics and, in particular, pharmacogenomics, which studies the role of the patient's genetic characteristics in the disorder of response to a drug [7]. At the same time, despite considerable achievements in the field of genomic technologies, the reduction in the cost of sequenation and testing by polymerase chain reaction, the creation of national programs for the development of personalized medicine, the evaluation of pharmacogenetic biomarkers for individualization of treatment has not yet been widely implemented in clinical practice. In addition to regulatory, administrative and financial barriers that were previously well described [8], the reasons for such a "failure" between advanced scientific achievements in the field of pharmacogenetics and real clinical practice is the lack of a solid system: the discovery of a new biomarker — the development of a test system — laboratory and clinical validation — the development of recommendations for use — clinical use; that is, the so-called "biomarker factory". The "biomarker factory" in this case refers to the division of the process of studying pharmacogenetic biomarkers into modules, where each participant or group of participants in the consortium is responsible for a certain stage. At the same time, all stages are closely linked and are part of one continuous process.

THE ROLE OF THE ASSOCIATION OF ACADEMIC CENTERS, CLINICS, BIOMEDICAL LABORATORIES, PHARMACEUTICAL COMPANIES AND OWNERS OF BIOBANKS IN BUILDING "BIOMARKER FACTORIES"

According to the Food and Drug Administration (FDA) Biomarkers, EndPoints and other Tools (BEST) glossary of terms, a biomarker is a characteristic measured as an indicator of pathological or normal biological processes or response to exposure or intervention [9]. Among the various types of biomarkers proposed by the FDA and the European Medical Agency (EMA),the following are primarily applicable to drugs: sensitivity (susceptibility) or risk biomarkers, prognostic biomarkers, monitoring biomarkers, pharmacodynamic biomarkers or response biomarkers, safety biomarkers. Biomarker development is a systematic multi-stage process in which the degree of reliability of evidence confirming the possibility of using a biomarker increases on the way from research in laboratory conditions towards clinical trials and actual clinical practice [10]. Schematically, the process of developing and introduc-

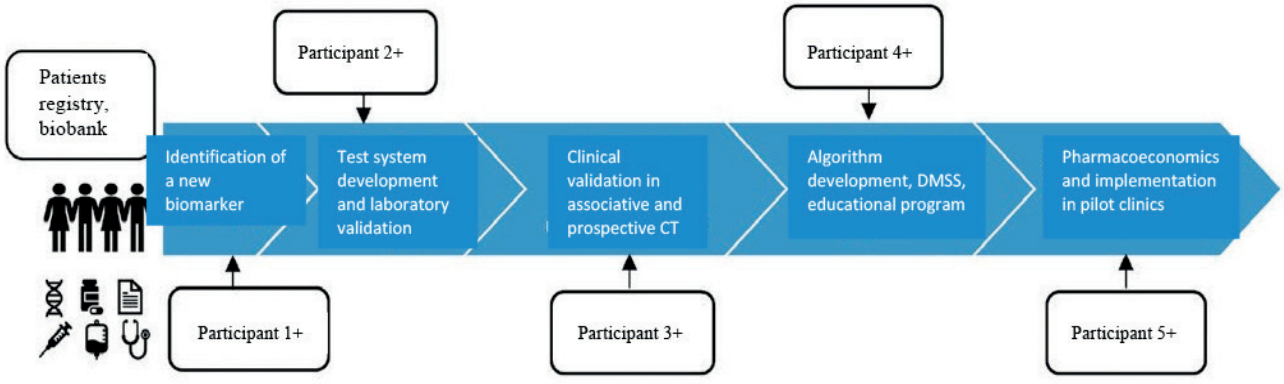

Fig.1. The structure of a "Biomarker Factory"

ing pharmacogenetic biomarkers, including new ones, consists of the following stages:

1. Justification of the need/demand for a biomarker.
2. Development of a reliable and reproducible methodology and test systems for biomarker measurement.
3. Biomarker validation on test and then on naive patient samples.
4. Development of an algorithm/scheme for using a biomarker to personalize therapy.
5. Prospective validation with an assessment of sensitivity, specificity, positive prognostic value, negative prognostic value.

After confirming the clinical usefulness of a biomarker for further implementation into clinical practice, it is necessary to develop computerized decision-making support systems (DMSS), educational programs, conduct pharmacoeconomic research (Fig.1).

Currently, in the context of the development of omics biomarkers and the collection of big data, the development and patent protection of individual biomarkers or the creation of paid separate databases of biomarkers (for example, genetic) without accompanying comprehensive clinical information about patients are increasingly less valuable, both for science and for the biomedical industry. Taking into account the growing number of open depersonalized databases with a huge array of omics patient data, the creation of an appropriate ecosystem around biomarkers by combining academic and scientific centers, biomedical laboratories and pharmaceutical companies, IT development companies and artificial intelligence into consortia plays an important role in the development and implementation of new pharmacogenetic biomarkers. Concurrently, academic centers with their infrastructure (genomic laboratories, collection of samples and databases of clinical data), clinical centers and educational competencies are increasingly becoming the most important component in the process of developing and implementing omics biomarkers [11]. At the same time, funding restrictions, the lack of the ability to quickly scale the infrastructure when new technological opportunities arise, the lack of strict regulatory requirements and advanced opportunities for the promotion of test systems at academic centers are effectively compensated by biomedical laboratories and pharmaceutical companies as part of the consortium.

Such associations of research groups can be formed around a specific problem or nosology. An example is the United Europeans multi-center research initiative for the development of pharmacogenomics in the treatment of multiple sclerosis (UEPHA*MS), a group of 11 research groups from 5 countries (Spain, Germany, France, Netherlands, Russia) to study biomarkers for the effectiveness of therapy for multiple sclerosis [12]. The European Union has allocated funding for UEPHA*MS in the amount of 2.3 million euros within the framework of the 7th Framework Program for Support and Promotion of Research in the European Research Area. UEPHA*MS was coordinated by the University of the Basque Country, Spain.

The prerequisites for the formation of UEPHA* MS were data for 2007 on 380 000 people suffering from multiple sclerosis, among 466 million people living in 28 European countries. At the same time, the total cost of patients with multiple sclerosis in Europe, as of 2005, was 12.5 billion Euros, of which 20% (2.5 billion Euros) was the cost of drugs [13]. Since treatment of multiple sclerosis with both first-line drugs (interferon beta and glatiramer acetate) and second-line natalizumb is effective only in some patients, there is a need to identify predictors of response to therapy. This need is also due to the significant economic and social burden of this disease for Europe, which affects mainly young people aged 20-40 years.

The UEPHA*MS team included experts in molecular biology, neurology, immunology, bioinformatics and computer modeling to study pharmacogenetic biomarkers of the effectiveness of interferon beta and glatiramer acetate drugs in the treatment of multiple sclerosis, as well as for the search for new biomarkers or targets for therapeutic effects in multiple sclerosis.

The main areas of work of the interdisciplinary network of experts in the field of pharmacogenomics in relation to multiple sclerosis UEPHA*MS were the following:

- development of clinical criteria and a collection of biomaterial; bases: clinics, including those at universities, interacting with each other;
- research in the field of genetics, transcriptomics, proteomics, cell biology; bases: research institutes and universities, as well as a biotechnology company developing diagnostic genetic tests, immunological tests for monitoring biological products, etc. ;
- statistical modeling and development of systemic approaches; bases: clinic where it is possible to analyze the response to immunotherapy, university (transcriptomic prognostic markers of therapy multiple sclerosis) and research institute (statistical analysis of the relationship between genes in the pharmacogenetics of drugs used in multiple sclerosis);
- experimental models and clinical trials; bases: research institutes and universities.

The primary task of UEPHA*MS, along with the scientific aspect, was to train young researchers in a new supradisciplinary field, which includes genomics, transcriptomics, proteomics, ”clinical science” and

"systems" biology. It is noted that training under the UEPHA*MS program will promote interaction and mutual exchange between fundamental and clinical translational research, between the academic environment and industry, as well as between laboratories in individual European countries. Eventually, students will gain skills that contribute to changes in the field of personalized therapy for multiple sclerosis.

In the future, the association within the framework of UEPHA*MS will form the basis of an interdisciplinary network of experts in the field of pharmacogenomics in relation to multiple sclerosis, which will allow participants to interact more easily to exchange knowledge and ideas. Experts note that despite the fact that most of the UEPHA*MS participants have already had experience of interaction with each other, their cooperation was previously spontaneous, since it was not systematized in the single network. This consortium, as planned, will combine within itself a collection of biomaterial of the required capacity, infrastructure, know-how and experienced scientists with the necessary set of competencies. Similar measures are presented in other areas: pulmonology — "Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes" (U-BIOPRED) [14], oncology — "Oncology" Research Information Exchange Network" (ORIEN) [15] and others.

Examples of the creation of such consortia have become increasingly common in the Russian Federation — the Consortium "Genetics of Cardiovascular Diseases" [16].

CONCLUSION

Taking into account the multicomponent character and complexity of the process of developing omics biomarkers, including pharmacogenomic ones, the need to create large repositories of samples with an accompanying database of clinical data, the need for flexible and scalable infrastructure, laboratory, clinical, educational and IT competencies, currently the most effective model for studying and launching new biomarkers on the market can be the creation of an ecosystem — a "biomarker factory" allowing to accelerate and systematize the path from the development of a new pharmacogenomic biomarker to its introduction into clinical practice.

Conflict of interest

The authors declare no conflict of interest.

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