Predictive Medicine Evolution

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ABSTRACT

Genetic Health Chart (GHCh) also known in the Russia as Genetic Pass (GP) is now considered as a major practical guide for predictive, preventive and personalized medicine (PPPM) which reflects basic achievements of human genome studies and makes major advances in line with spectacular advances of molecular technologies of human genome endeavor. Since its birth in 2000 GP has been treated as a bank for collection of personal genetic data important for prediction, prevention and for treatment of inherited and inborn disorders. Major steps of PPPM, its main problems, disappointments and advances as well as their impact in evolution of GP are briefly outlined. The basic goal of the currant genomic studies as emphasized concerns the urgent need for correct interpretation of the clinical value of genetic testing and its applicability for routine clinical practice. Feasible paths towards the gradual implementation of personal genetic data, in line with other laboratory tests, for the individualized clinical trials are discussed.

Keywords: Genetic Health Chart; Personalized medicine

INTRODUCTION

The review is devoted to the impact of human genome studies in the progress of modern medicine. Basic achievements of genome research have resulted in the deciphering human genome (2003) [1] and molecular landmarks dispersed throughout haploid genome (HapMap Project) (2004) [2], has made a tremendous contribution into our knowledge of common genetic and complex disorders. Initial genetic researches were mostly devoted to identification the genes and their mutations responsible for monogenic disorders. Current genome studies mainly focus on genetic testing and its associations with common diseases for their efficient diagnostics, prevention and personalized treatment [3].

Identification of candidate ("predisposition") genes in the functional genetic modules underlying each common disorder and the use the genetic background for their prevention constitutes a major goal of personalized molecular medicine [4,5].

The concept of genetic pass (GP) as an personal DNA databank reflecting inherited human predisposition to different complex and monogenic disorders, with special emphasis on the state of art, and numerous difficulties related to the practical implementation of personalized medicine has appeared in early 2000 in conjunction with already recognized predictive, preventive personalized medicine initially called 3P Medicine [6,7]. One more “P” was donated from "participatory" suggested in 2008 by Leroy Hood (USA) thus giving rise to 4P Medicine (Figure 1).

Predictive medicine

In 2004 National Institutes of Health recommended replacing “personalized medicine” with “precision medicine,” later converted into genomic or individualized medicine. All these names rather similar by sense - medical care should stem from the unique patient’s biology, determined by the genome. The concept of 4PM was suspected to revolutionize clinical and preventive patient care.

The problems related to the uncertainty of the results of genetic testing could be overcome at least partly by means of new molecular technologies, such as genome-wide association studies (GWAS), massive parallel DNA sequencing, next generation
sequencing (NGS), genetic and epigenetic profiling. The basic
tasks of genomic today could be attributed to proper evaluation
the practical value of genetic testing and its applicability for the
clinical benefit. Successive steps of progress in genome
technologies as well as these ones in medical genetics are shown
in Figure 1.

Figure 1: The schedule of principal human genome studies advances
(left) and basic steps in the progress of medical genetics (right).

Over 1500 candidate genes associated with common diseases
were picked up in human genome by functional gene mapping
in many European populations summarized by Gendia (http://
www.gendia.net) (Gennovation (www.gennovations.com),
Genosense (http://www.genosense.com), as well as by many
genetic centers in the Russia (Saint-Petersburg; Tomsk, Ufa,
Moscow e.a., [7-9]). Hundreds candidate genes associated with
many common and monogenic disorders were also tested in our
laboratory at the Ort’s Institute of Obstetrics, Gynecology &
Reproductology in Saint-Petersburg. Original Copy of the Gene
Pass as a natural synopsis of predictive genetic testing is shown
in Figure 2.

Personal Genetic Chart (Pass)

Figure 2: The copy of the Gene Pass originally suggested in Saint-
Petersburg 2000 [7].

Much more enriched candidate gene charts were later suggested
by many commercial genetic centers in the Europe, North
America, also in the Russia and widely used for genetic profiling
of direct to consumer testing. Unfortunately high rise of
enthusiastic wave quickly subsides and converted to the plateau
of deep disappointment provoked by negligible prognostic
values of routine genetic testing. Contrary to monogenic
disorders with their mutation testing precision close to 100%
the values of genetic testing of common disorders usually does
not exaggerate 1-2% thus being far from sufficient to cogent
prediction.

Two main faults of comparative gene testing have been
suspected: shortage of candidate genes identified by physiologic
gene mapping (1), insufficiency of cohort quantity (2).

According to our data Gene Pass testing can at its best predict
whether the patient belongs to the risk group of some common
disease but they are not sufficient to predict the onset of the
disorder in particular person. Thus the results of paired
candidate testing in the patients if compared to these ones in
healthy specimen looked very scanty. Illusion to overcome this
obstacle come with implementation of new molecular
technology – Genome Wide Association Studies (GWAS) which
for the first time provided whole genome screening of candidate
genes in abandon cohorts of patients and the control
counterparts. Thus it looked very plausible that GWAS
technology will solve principal task of predictive testing, making
much more reliable prognostic values. But expected miracle has
not happened. Actually application of GWAS technology
significantly increased the number of candidate genes for each
of 300 CD studied by this technology but the prognostic values
of GWAS tests still were within merger ranges 10-25% at the
best (Figure 3).

Figure 3: Genetic arrays adopted for predictive genetic testing of
common diseases The gene sets provided by extensive studies of
biobanks collections (GeneSKit, Systemas Geneticos etc ). After DNA
sequencing by NGS technology the data are subjected to relevant
bioinformatic analysis further supplemented with interpretation by
means of Electronic Health Records (EHR), and Global Clinical
Decision Support System.

Predictive value of these complex amplise-arrays technology still
remains unknown and needs further verification.

The obvious phenotypic shortage of hereditary information
gained the term “missing heritability” [10,11]. Several main
reasons of this discrepancy are suspected. Small risk values of
unfavorable alleles (OR -1.1-1.5) (1). GWAS does not detect
SNP polymorphisms with low frequencies (<0.5%) (2). Inter
genetic SNP associated with common disorders (CD) are not correctly interpreted (3). Gene-gene interactions (epistatic effect) not properly considered (4). Epigenetic & VNTR variations were not taken into account (5). Underestimation of exogenetic damages (6). Taken into account listed limitations makes clear that GWAS by itself a priory is not sufficient for objective predictive testing. Moreover it looks that DNA analysis by itself will never be sufficient to reach 100% confidence of predictive value [12].

These considerations are in line with genetic twin studies. In spite of genetic identity monozygote twins differ in frequency of many complex traits (i.e., height) as well as in frequency of CD. It means the development of complex traits and CD should be attributed to both genetic and epigenetic interactions.

Thus the search for dominant unfavorable alleles, relevant considerations of CNV input, gene-gene interactions and epigenetic regulation of genome functions are obvious mainstreams in missing heritability study [12].

System Genetics & Integrative Omics

New option for the further advancement of PM should be addressed to implementation of DNA sequencing. According to Eric Lander (Massachussets Inst. of Technology) implementation of NGS in conjunction with abandon cohorts of patients should be the most efficient way for cutting the Gordiev helix of “missing heritability” [13]. The accuracy of nucleotide variation detection supplemented with relevant bioinformatic analysis provides ample opportunities for precise detection of all nucleotide fluctuations both meaningful and senescent. In 2017 FDA Committee (USA) discarded its former order to seize prognostic genetic testing by American genetic company 23andMe. The company resumed commercial gene testing for 10 common CD (Crome, Alzheimer, Parkinson diseases, prostate and breast cancers [13]. Genetic testing is also used for detection of inherited predisposition to over 100 CD by means of system genetics approach [14]. The precision of genetic testing increased to 20% for prostate cancer and up to 80% for Crome disease. Testing of hundreds genes with assistance of high density arrays was a main prerequisite of this obvious success [15-17].

Massive gene testing gained more knowledge in the mapping of many new CD genes and gene regulation loci of substantial commercial value. So called “black-chain technology” now gets big financial support from many commercial companies and pharmaceutical industry destined for production of targeted drugs and personalized treatment [18]. But increase in number of tested genes does not much improved predictive gene testing efficiency. Comparative analysis of functional activity of candidate genes expression in normal and abnormal development should be taken as the best way to understand the genetic architecture and thus the pathogenic of common disease [9]. Each separate technology cannot give objective view of pathology but their integrative approach might be rather fruitful. The integration of different omics data (genome, transcriptom, proteome, metabolome) also known as system genetic approach (Figure 4) is now widely used in molecular medicine [19].

Thorough Network analysis of different omics significantly increases the chances to find new biomarkers and new candidate genes [20]. Integration of protein data, NGS and SNP – GWAS results is now tried in studies of heart diseases, diabetes type 2, autism. System genetic approach is now considered the best to understand integrative genetic architecture of CD and it becomes dominated in PM on its way to Precision Medicine [21].
According to European PPPM Organization Program [6] as the first step of its pathway PPPM should rely on massive NGS of human genomes to clarify their population, ethnic, social and inter-tissue specificities. Concomitantly integrated longitudinal omics profiles should be compared with relevant clinical traits and laboratory analysis of the same patients thus creating integrative personal gene sets of affected organs and physiological systems. All these data as expected much enrich the capacity of PPPM. Moreover each patients in this system becomes a source of valuable information for the further in depth studies [6]. On the other hand the pathway program prefer to deal not with the patient himself but only with his models in virtual world does not looks robust as no any model can ever completely mimic all features of original subject [22,23]. To our mind the term "precision medicine’ is illusive and misleading as the medicine according to classical definition should be treated an ART not a SCIENCE (If not for the great variability among individuals, medicine might have been a science and not an art.” Sir William Osler (1849-1919).

Probability not Determinism governs basic concepts of Medicine and the same stands true for Predictive Medicine. But whatever happens the Genome is always a solid ground of the Personal Life. The Era of Predictive Medicine has arrived!

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