Dušica BABOVIĆ-VUKSANOVIĆ*

GENOMICS: MODERN FORTUNE TELLER

Abstract: Genetic science has evolved over the last century and has become integral part of everyday medical practice. Instead of its initial use as a diagnostic tool to explain condition or confirm clinical suspicion, we see genomics more and more providing information to be used in predictive and preventive purposes. Genetic testing is now widely available, as the price of testing has become more affordable. Determining genetic predisposition for disease often result in preventive measures that can avoid development of disease or in screening programs that can detect disease in early stage when treatment is more effective. In addition, genetic information may guide treatment by selecting appropriate medication and dose for the individual patient. Genetics may be seen as a modern fortune teller!

Key words: *genetics, genomics, sequencing, predictive medicine, preventive medicine*

INTRODUCTION

Prevention and cure of disease, longevity and immortality have been human dream for centuries. They used culturally specific spiritual, religious theories and self-educated healers and fortune-tellers. As environmental factors, such as availability and quality of food, wars, infections and toxic exposures have been gradually eliminated as primary influencers in survival and human wellbeing, at least in the developed world, more and more attention is now directed to genetic factors as main determinants of our outcome.

The discovery of the double helix structure of deoxyribonucleic acid (DNA) by James Watson and Francis Crick in 1953 marked a milestone in the history of science. Only 50 years after their discovery, the genetic

* Dušica Babović-Vuksanović, MD, Professor of Medical Genetics and Pediatrics; Consultant, Department of Clinical Genomics, Mayo Clinic, Rochester, MN, USA; Director of Neurofibromatosis Comprehensive Program, Mayo Clinic

code was revealed by completion of the Human Genome Project in 2003. The $3 billion, 15 year endeavor described the 2.85 billion nucleotides and 20,000–25,000 protein-coding genes comprising a human genome. Since that breakthrough, the last quarter century has been marked with fast and productive development of technology, bringing genomics into medical practice and revolutionizing how we practice medicine.

MAIN TEXT

Medical practice has for long time followed the classic model of reactive medicine, where a sick patient seeks treatment for symptom relief. In this way many conditions are diagnosed too late, when treatments are not effective. Drugs have typically been given based on patient's age, weight and possible drug interactions. Now, with emerging genomic information, the concept of precision medicine and individualized approaches in diagnosis and treatment has been rapidly advanced. We are trying to predict susceptibility in order to prevent disease and develop novel, targeted treatments. We want to move away from fortune-teller strategies.

The development of rapid sequencing methods coupled with lower price and improved computing models for analysis, allowed for increasing utilization of genetic information and set the stage for personalized medicine. Now, large gene panels or whole exome or genome sequencing has become the first line diagnostic test for many phenotypes. Once the genetic cause of disease is identified in the individual patient, it may serve as tool for predictive testing for others in the family. This can facilitate early detection and more effective therapy or even preventive measures. Familial cancer syndromes, such hereditary breast and ovarian cancer, Lynch syndrome, and Li-Fraumeni syndrome are all cardinal examples.

As sequencing tests analyze more and more genes, the possibility of detecting incidental findings has increased, and the debate was opened about appropriateness, ethical and legal aspects of reporting the secondary finding. The American College of Genetics and Genomics (ACMGG) has issued recommendations for actionable conditions that should be reported to patients, which could be considered as the opportunistic screening for selected variants that could influence medical management [1]. These guidelines have been widely adopted by diagnostic laboratories.

Pharmacogenomic (PGx) applications are rapidly becoming an integral part of modern practice with many validated examples of the clinical utility. Both common and rare pharmacogenomics variants may inform individualized drug selection and dosing. This type of clinical genomic information is increasingly being generated in clinical laboratories, incorporated

into electronic health records, and used to „tailor“ or individualize drug therapy [2]. The inclusion of PGx results as a secondary (actionable) findings in WES testing is still not a common practice due to additional challenges related to technical problems (pseudogenes, haplotypes composed of several variants, incomplete coverage of intronic sequence), complicated „star allele“ nomenclature and challenges in implementing PGx results into wide clinical practice due to lack of competencies in interpretation of these results. Also, some have argued that PGx results are not actionable until the decision is made to prescribe a drug related to the particular variant [1]. On the other hand, our experience has suggested that these incidental findings are often highly relevant. IN our series of WES results on 94 young patients with median age of 10 years, a subset of PGx variants in *CYP2C19*, *CYP2C9*, and *VKORC1* were reported. The majority of tested patients had dominant neurological pathology (71%), and was currently taking medications (90%). Of the 94 PGx-evaluated patients, 91% had at least one variant allele reported and 20% had potential immediate implications on current medication use [3]. Therefore, decision about selecting the patient-appropriate test, with or without components such as PGx or secondary results should take in account multiple factors including indication for testing and clinical scenario.

There is also a growing interest for application of genomics in predictive testing of healthy individuals and population screening, which remains controversial due to high risk of result misinterpretation especially in direct-to-consumer genetic testing, without involvement of qualified genetic This concern led to the ACMG Statement on Direct-to-Consumer Genetic Testing, highlighting that it is critical for the public to realize that genetic testing is only one part of a complex process that includes genetic risk assessment, diagnosis, and disease management [4]. Due to potential for performing DTC testing in minors, the AAP and ACMG published the statement which strongly discourage the use of direct-to-consumer and home kit genetic testing of children because of the lack of oversight on test content, accuracy, and interpretation. They also highlighted need for caution with predictive and carrier testing in children [5, 6, 7].

Despite rapid development of genomic-based medicine and widespread use of genetic information in medical practice, it cannot replace expert clinical phenotyping and use of classical medical and genetic principles. The family history analysis had been a primary tool that physicians have used to estimate genetic predisposition for illness, and detailed phenotyping has been a foundation for clinical diagnoses. These tools continue to play a fundamental role in a genetic practice. Development of new automated tools

for analysis of genetic information did not eliminate them, but has even increased its value in interpretation of complex or ambiguous genetic data, which can only be understood based on correlation with clinical information and segregation of disease phenotype with genetic change [8].

Lately, we are facing spectacular headlines of human ability to clone animals (maybe including humans), correct genetic alteration in embryos and perhaps even be able to choose certain traits in our offspring by manipulating DNA. There remains constant argument between pro-futuristic and risk-taking proponents who see the genomic progress as a holly-grail of human outcomes and medical progress, and those who express concerns about consequences of premature overuse of genomic information and lack of scientific evidence to guide its application. The healthy and balanced argument is needed to crystalize directions and allow comfortable entry of genomics in radical change how we will practice medicine in the future [8].

With all of the fascinating and rapid progress in genomic science, the education of providers and the public regarding appropriate use, limitations, risks and benefits is paramount and one of most important factors in bringing genomic medicine to full utilization. Rapid pace of these advances is opening the gap between the knowledge available about the clinical relevance of genomic information and the ability of clinicians to include such information in their practices. The educational gap threatens to be rate limiting to the clinical adoption of genomic medicine. This prompted National Human Genome Research Institute to initiate development of genomic practice competencies for physicians in various medical disciplines [9].

CONCLUSION

Wise and evidence-based use of genomic tools will certainly continue to transform medical practice and take us much further away from crystal ball fortune-tellers and towards modern, safe and reliable personalized medicine.

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Dušica BABOVIĆ-VUKSANOVIĆ

GENOMIKA: MODERNI PREDSKAZIVAČ BUDUĆNOSTI

Sažetak

Genetika je doživjela veliki napredak u zadnjih 100 godina i postala integralni dio svakodnevne medicinske prakse. Umjesto upotrebe genetskih testova samo za postavljanje dijagnoze, danas se genetska informacija sve više koristi u preventivne i prediktivne svrhe. Sa smanjenjem cijene testova, genetsko testiranje je sada dostupno u svakodnevnoj praksi. Saznanje o nečijoj genetskoj predispoziciji može da rezultira u prevenciji bolesti ili u uspostavljanju dijagnoze u ranom stadijumu bolesti kada je izlječenje još moguće. Nadalje, genetska informacija može da služi za izbor lijeka i doze koja odgovara svakom individualnom pacijentu. Genetika postaje moderni predskazivač budućnosti!

Ključne riječi: *genetika, sekvenciranje, prediktivna medicina, preventivna medicina*