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Precision Medicine for Endocrinology

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In the recent decades, major biotechnological advances have been achieved following the sudden escalation of disease-related molecular information, with the potential for greatly advancing patient care. The human genome was depicted in year 2000, followed by the completion of the human genome project in 2003. Scientists have ignited a firestorm of breakthroughs in genomic information, by laying out, in order, the 3.2 billion units of human DNA. Innovative genomic technologies including whole-genome single nucleotide polymorphism (SNP) chips, RNA interference high-throughput screening, microarrays and next-generation sequencing have also rapidly surfaced offering enormous potential in this field. This genomic revolution era offers unlimited possibilities and unlimited possibilities including the development of individualized medical necessities for each human, based on his unique genomic information (1).

Currently, personalized medicine is commonly defined as a combination of molecular profiling and traditional diagnostic and therapeutic strategies, precisely adapted to the individual requirements of patients (2). The fundamental idea behind personalized medicine is to couple large amounts of data available from the human genome with established clinical-pathological indexes to devise diagnostic, prognostic, and therapeutic policies specifically adapted to each patient needs and the ensuing research wave of the molecular basis of disease. Eventfully, precision medicine facilitates more accurate diagnosis and therapy at the intrinsic molecular level, promoting the individual bation and this allows the customization of healthcare and incorporation of electronic medical information obtained both on an individual and on a more comprehensive global scale (3).

The success of precision medicine faces many challenges. First being the establishment of frameworks for organizing, compiling, and elucidating the influx of data that can keep in pace with rapid scientific innovations. Second, the shift toward a deeper understanding of disease, based on molecular biology, necessitates reclassification of disease states incorporating this knowledge, i.e. modernization of the world health organization's international classification of diseases, for which there is a need for a reconsidered categorization classification based on intrinsic biology and traditional signs and symptoms. Thirdly, precision medicine will require promotion of handling of multi-parametric data and some proficiency in interpreting "-omics" data, dealing with the anticipated complexity and volume of new information. Addressing these challenges will require effective clinical decision support tools and new educational models (4).

It is anticipated that the initiative for precision medicine has two main components: 1) A near-term focus on cancers and 2) A long-term objective to generate data pertaining to all aspects of health and disease. This requires keeping upright research advances that will facilitate better evaluation of disease risk, comprehension of pathophysiology and prediction of favorable treatments for many more illnesses, with the aim of expanding the advantages of precision medicine into innumerable aspects of health and health care, which will undoubtedly motivate the next generation of scientists to develop novel innovative approaches for identifying, measuring, and analyzing a wide range of information data, including molecular, genomic, cellular, clinical, behavioral, physiological, and environmental frameworks (5).

The question that remains to be answered is whether it is possible for the concept of precision medicine to be extended to endocrine disorders. Let's consider diabetes, a disease that is today a major health problem worldwide and an epidemic in 21st century. It has been estimated that there are 330 million people with diabetes worldwide, almost half of whom are undiagnosed (6). This disease is a major cause of cardiovascular disease, renal failure, blindness and non-traumatic amputation and is the seventh

leading cause of mortality (7). It is noteworthy to mention that these figures are not only for developed countries, yet the prevalence of diabetes in many developing countries is increasing, and has imposed considerable medical expenses on the health budget. In the Islamic Republic of Iran, a developing country in south-west Asia, with 76 million population, the estimated diabetes population has increased from 3.6 million in 2005 to 4.5 million in 2011; corresponding figures for pre-diabetics have been 4.4 and 5.8 million, respectively. In Tehran, incidence rate of type 2 diabetes has been 1% per year. Diabetes mellitus among males was ranked number 25, 13 and 22 for years of life lost (YLLs), years lost due to disability (YLDs) and disability-adjusted life years (DALYs) in 1990 and 12th, 5th and 10th in 2010, respectively. Diabetes as a cause of death has increased by 40% in the last 20 years (8).

There has been great progress in understanding of the pathophysiology and management of diabetes. However, despite availability of several classes of drugs for diabetes, both oral and insulin preparations, treatment is often on a trial and error basis or on the availability or affordability of medications, rather than the underlying pathophysiology; hence most diabetics do not achieve proper blood glucose control (9), mainly because all guidelines aim at management of an average patient, rather than at personalized, precision medicine. With increasing knowledge of the molecular causes of diabetes, we need to increase and update our tools for identifying patients at very early stages, even before pre-diabetes, to begin early preventive measures to abort or delay the onset of the disease. The advent of precision medicine for diabetes will require handling, incorporation and interpretation of massive amounts of genomic, metabolic, lifestyle, environmental, and clinical and para-clinical data, all of which need comprehensive investigations, progressive education and manpower training (10). With rapid progression of related sciences, there is prediction for near appearance of precision diabetes clinics (11).

Another example of the impressive benefits of precision medicine in endocrinology is the treatment of thyrotoxicosis. Anti-thyroid drugs have been the mainstay of treatment of hyperthyroidism for years. However, with fixed doses of this drug, some patients become euthyroid, some develop hypothyroidism and others still remain hyperthyroid after a few weeks. In addition, if anti-thyroid medications are given to pregnant women in the first trimester of pregnancy, although safe for most, it causes fetal malformation in some (12). So, would it be possible to identify the exact dose of anti-thyroid medication for each individual patient and avoid giving it to the pregnant women, whose genomic and molecular study shows definite possibility of adverse effect on the fetus? Some scientific developments have taken the first steps towards precision medicine for anti-thyroid drug-induced agranulocytosis (13).

Pharmacogenomics is the study of how a person's reactions to medications are affected by their genetic constitution. It integrates pharmacology and genomics to develop efficient, safe medications and doses individualized to a person's genetic makeup. A sub-discipline of functional pharmacoproteomics is a study of how the protein content of a cell or tissue changes qualitatively and quantitatively in response to treatment of disease, and how a person's protein variants in quality and quantity affect a person's reaction to a medicine (14). Using this technique in precision medicine may help answer the challenges of anti-thyroid therapy, such as what has been proposed for metformin pharmacogenomics (15).

It must be accepted that some people from the medical community feel that unstinting focus on precision medicine is a mistake and a diversion from the main aim/target of producing a healthier population; they are not convinced that investing in biomedical research will result in unlimited rewards in finances and the health of people, and they emphasize that the challenges we are confronted with to improve population health do not include the frontiers of science and molecular biology; for them, it requires development of the scope and will to address certain incessant social realities, and an unstinting focus on factors, indispensable to the production of population health (16). They worry that an openhanded focus on precision medicine by trusted spokespersons for health is a mistake and a distraction from the goal of producing a healthier society in reality; health care stakeholders must be made aware that precision medicine is no longer just a blip on the horizon and ensure that it lives up to its promise.

Endocrinologists are called upon to participate and take part in the development of precision medicine for endocrine disorders and the management of their patients, by accepting the complexities and heterogeneities of these disorders and their burden on population health (10, 11, 17, 18). This will be a worthwhile investment with significant positive medical and socioeconomic outcomes for achieving "health for all".

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