SHORT COMMUNICATION

Precision medicine in non-communicable diseases

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ABSTRACT

One of society's biggest accomplishments throughout the 20th century was the extension of life expectancy, which resulted in a dramatic rise in the proportion and number of elderly people in almost every nation on earth. One of the main effects of this phenomena is the load of chronic diseases, which drastically reduces elderly people's quality of life and puts pressure on the effectiveness and sustainability of healthcare systems. Non-communicable diseases (NCDs) are regarded as a global emergency because they cause more than 70% of fatalities globally. Additionally, complex and multidimensional disorders including hypertension, diabetes, and obesity are caused by NCDs.

NCD epidemics are a result of complex interactions between development, economic growth, and health. The genetics, microbiome, metabolome, immunological state, and environmental elements like dietary intake and chemical exposure all participate in this process. Therefore, it is crucial to create a novel, customised, preventative, and early care strategy to combat NCDs by integrating different molecular profiles of people to find both the crucial biomarkers of NCD vulnerability and novel treatment targets.

Key Words: *Precision medicine; Genomics; Epigenetics; Pharmacogenetics; Genomic biomarkers*

INTRODUCTION

The most recent development in modern medicine is precision medicine (PM). PM strives to investigate the human being as uniq--ue and unrepeatable, the specific mechanisms that determine the diseases, and the most effective preventative and therapeutic measures using vast volumes of data about people's health, individual traits, and living circumstances [1].

Precision medicine is now a model for illness prevention, diagnosis, and therapy based on the patient's genotype in many human genetic diseases because to recent advancements in genetic sequencing tools. This concept has been used specifically for the treatment of cancer and is relevant to non-communicable disorders (NCDs).

As the leading danger to the long-term viability of healthcare systems, NCDs are the most feared killer, accounting for 70% of all fatalities. Cardiovascular disease, diabetes, cancer, neurological diseases, and chronic respiratory illnesses are the primary NCDs. NCDs are the third-highest hazard in terms of gravity on the World Health Organization's list of the top risks to global health in 2019.. In fact, millions of people worldwide are afflicted by NCDs such obesity, diabetes, and hypertension [2]. NCDs are caused by complex interactions between predisposing genetic traits (at the individual and population level) with other factors such as indiscriminate urbanization, pollution, climate change, unhealthy lifestyles, and aging. In order to tackle these diseases, a coordinated and systematic approach to risk assessment that considers both a person's genetic profile and the examination of particular environmental factors (such as membership in a particular socioeconomic group) may be useful. According to estimates (source: WHO), implementing measures to prevent and combat NCDs might result in economic growth of up to USD 350 billion for low- and middle-income countries by 2030.

INSUFFICIENCIES OF MODERN MEDICINE

More than 25 percent of medications that start the clinical development process fall short due to inefficiency .Only a small percentage of individuals benefit from other medications that are introduced to the health market. In many instances, the outcome is what causes current medical therapies to fail [3]. Disappointing outcomes when employing medications outside of research trials in actual clinical care are caused by a variety of factors. To ensure drug delivery and adequate drug dose exposure at the site of action in early clinical development, more research and innovation are needed. It's possible that nanotechnology, modelling, and simulation within in silico trials will help in addressing the complexity of real drug exposure in a clinical setting. Additionally, in the past, the majority of pharmaceuticals created through clinical trials were mostly based on the typical outcomes in sizable populations that were "clinically" homogeneous [4]. The growing taxonomy of diseases that takes into account disease heterogeneity (particularly in cancer) as well as clinical and genetic patient variability has significantly increased the difficulty of this approach. Therefore, it is crucial to take use of new

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scientific discoveries and technology, particularly in the fields of genetics, omics, and immunology, in order to redefine the eligibility requirements and create and carry out creative clinical trials. In order to offer the necessary real-world data and proof to establish not just efficacy but also effectiveness and actual value, the outcomes recorded during development are then to be repealed as a continuum in actual clinical treatment.The information learned about the human genome after the year 2000, the findings of studies on its variation, and the more effective and reasonably priced modern sequencing functional technologies have made it possible to:

In some situations, it is also possible to define the genetic component influencing an individual's reaction to pharmacological therapy, as well as the gene sequences implicated in the activity and toxicity of medications [5]. Analysis of inter-individual variations in DNA sequence and expression is currently a choice method for comprehending and predicting the diversity of drug response. For this reason, the genetic basis of individual response heterogeneity has drawn the interest of the pharmaceutical industry, academia, doctors, and regulators.As a result, both clinical drug research and clinical practise have changed from population-based to more customised therapy [6]. The study of genetic and epigenomic elements that affect medication pharmacokinetics (PK) and pharmacodynamics (PD), as well as drug-drug interactions, is the cornerstone of pharmacogenomics, a key tenet of "personalised medicine" (DDIs). Examples include QT prolongation (drug safety), cancer, HIV, and cystic fibrosis (drug efficacy), as well as cytochrome P450 enzymes and CYPs (drug PK) . By including pharmacogenomic data in the summary of product attributes, knowledge of genomic variation is now converted into clinical use (SmPCs).

GENOMIC BIOMARKERS FOR NON-COMMUNCABLE DISEASES

In addition to offering new targets for early disease diagnosis, drug discovery, and drug development, the growing body of knowledge about the genetic basis, pathogenesis, and therapeutic potential of NCDs also suggests methods for putting this knowledge into practise in the form of (initial) clinical trials. Biomarkers are a quantifiable biological sign that can offer data on NCD risk assessment, diagnosis, and treatment. It is possible to find novel biomarkers for characterising and comprehending the molecular basis of NCDs using omic sciences (genomic, transcriptomics, proteomics, and metabolomics). A genomic biomarker (GB) is a detectable DNA or RNA property that serves as a biomarker for pathogenic processes, therapeutic response, or other biologicalprocesses.

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An example of a genomic biomarker would be one that reflects the control of a gene, its expression, or its function. Proteomics is not a genetic biomarker metabolomics, or both. In the past 25 years, GBs have transformed the study of NCDs by identifying pathophysiology, prognosis, individual risks, population hazards, and, most recently, therapy. GWAS investigations have helped to identify several of these GBs. Additionally, GBs have opened up a new field of study called epigenetics by helping us better understand the relationships between genotype and environment. Epigenetics and high-throughput omics sequencing have in fact begun to reveal mechanisms linking multi-organ response to stressors such as exercise, diet, relationships and emotions,and the environment.

These overlapping sciences are yielding evidence that is extremely complicated and frequently lacks connections that call for additional research endeavours. In order to guarantee the robustness and repeatability of the results across research, the scientific community is currently accepting the task of beginning the establishment of reference standards . According to NIH [7], it is now widely acknowledged that individual heterogeneity in genes, environment, and lifestyle should be taken into account when developing disease therapies and preventative strategies. This, in turn, requires the definition of patient groups/individualization to decide on whether to treat or what dose to use to estimate response and toxicity to a given treatment, decide what “drug-cocktail” is most “promising”, and finally which companion diagnostics (CDx) is needed for GB detection. Patients with particular EGFR mutations have better survival status than those without, indicating the benefit of TKI therapy. Individuals harboring somatic mutations in *TP53, LRP1B, STK11, KEAP1, BRAF, MET,* and *MRC2* had significantly shorter survival time than individuals with wild-type, which suggest that mutations in these genes can be used as prognostic GBs in clinical practice.

Three unique molecular subtypes of oesophageal cancer with potential therapeutic relevance have been identified by researchers using molecular markers [8]. HLA-C*06:02 genotype is a GB of biologic therapy response in psoriasis. Adalimumab performs better in HLA-C*06:02-negative patients than ustekinumab [9]. Cardiovascular illnesses, diabetes, Parkinson's disease, age-related macular degeneration, inflammatory bowel diseases, autism spectrum disorder, and schizophrenia are other examples of NCDs when the use of GB for diagnosis or treatment selection is applicable [10]. According to the identification of rare alleles, these instances are expected to rise in the upcoming years . As an illustration, Dwivedi et al. demonstrated that a rare loss-of-function allele, p.Arg138*, in the SLC30A8 gene encoding the zinc transporter 8 (ZnT8), which is enriched in Western Finland, protects against type 2 diabetes (T2D) . This last example represents a model in our opinion of the translation of a GB discovered during research to clinical practice. A good model for which GBs affect diagnosis and therapy is represented by rare diseases and, in particular, neuromuscular diseases.

CONCLUSIONS

The epidemic of NCDs is the result of intricate interplay between genetic factors affecting both individuals and the population, as well as global phenomena as population ageing, inadequate globalisation of unhealthy habits, urbanisation, and climate change. All of this necessitates a fundamental shift in the care delivery paradigms currently in use around the globe as well as the creation of new prevention and intervention protocols on a global scale using new technologies, new educational frameworks, new financial tools, and novel forms of cooperation and interaction between the various actors (governments, universities, patient associations, industry, civil society). Most nations anticipate that national health spending will continue to increase at a rate that rate that is faster than their GDP. Numerous systems will soon become unsustainable due to expansion and rising healthcare expenditures. Even if a long-known medicine like insulin were to become available, these prices in developing nations would still be unaffordable. Instead of falling in recent years, the price of insulin has tripled. Recent developments have significantly improved health outcomes, but they have also given rise to new technologies and services that raise the expense of healthcare.

Additionally, increased standardisation of health services, together with more efficient and integrated patient treatment and prevention initiatives, might significantly lower costs and improve quality because the NCD population accounts for the majority of healthcare spending. Without a doubt, primary and secondary prevention are the only long-term solutions to the sustainability issue. Therefore, it is crucial to implement cutting-edge health policies for the management of NCDs in order to minimise their negative effects on public health.

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