Bioinformatics Shape Personalized Medicine: A Perspective

Manisha Rana

Department of Forensic Sciences, Amity University, Noida, India, rana.manisha1493@gmail.com

***Corresponding author:** Manisha Rana, Department of Forensic Sciences, Amity University, Noida, India, Email:rana.manisha1493@gmail.com

Abstract

The advent of systems biology as a comprehensive science has led to recent developments in high-throughput technology to achieve more accurate simulation of complex diseases. Many expect the advent in the near future of personalised medicine. We are however, transitioning to a two-tiered personalised medicine from two-tiered health systems. Personalized medicine can be generally defined as a predictive, personalised, preventative and participatory healthcare model. The bioinformatics field will be inundated with individual genomic data in the coming years. This data flood poses critical issues that need to be addressed by the bioinformatics community.

Introduction

In order to better understand biological processes, access to broad omics data (genomics, transcriptomics, proteomics, epigenomics, metagenomics, metabolomics, nutriomics, etc) has revolutionised biology and contributed to the advent of system biology. Systems biology attempts to model dynamic biological interactions through the holistic incorporation of knowledge from interdisciplinary fields (holism instead of the more traditional reductionism). In contrast to treating a mixture of variables as single entities leading to an endpoint, in order to provide mechanistic insights to an endpoint, systems biology relies on experimental and computational approaches [1]. Traditional observational epidemiology or genetics alone is not adequate for multifaceted heterogeneous disorders to be completely elucidated and this explicitly restricts all pursuits of prevention and care for such diseases [2,3].

To refer to genomic medicine, the term' personalised medicine 'is widely used. It is known as the use of genome knowledge (from humans and other organisms) and its derivatives (RNA, proteins and metabolites) to direct medical decision-making. It is generally accepted that to gain understanding of biological processes, several dimensions must be considered simultaneously [4]. The leading-edge approaches to processes drive biology and medicine [5,6]. The use of deterministic networks for normal and abnormal phenotypes is believed to allow predictive, preventive, personalised and participatory medicine for the proactive conservation of well-being relevant to the individual (P4, or more generally speaking, personalized medicine) [1].

In the near future, many expect the advent of personalised medicine, but it is not likely to happen as soon as the scientific community and the media will assume [7]. A similar two-tiered pattern is observed in relation to our ability to produce and interpret omics data, which could further delay the transition to personalised medicine, in parallel to an escalating two-tiered health system at the global level. Despite technological advancements, the generation and management (storage and computational resources) of omics data remains costly. This suggests that the wealthiest nations could be limited to personalised medicine [8]. This is expressed by a rising gap in our ability to produce and interpret data from omics. In omics approaches, the bottleneck is becoming less and less about the production of data and increasingly about data management, integration, analysis and interpretation [9]. There is an urgent need to bridge the gap between developments in high-throughput technology and our ability to process, incorporate, analyse and interpret OMICS data [10-12]. This analysis addresses the growing gaps in the progress towards personalised medicine in socioeconomic and scientific terms.

The Personalized Medicine Promise

The idea of Personalized medicine promises to move to future healthcare systems with a more proactive

and predictive approach to medicine, where the focus is on prevention of diseases rather than symptom treatment. At the heart of this strategy would be the individualization of care for each patient, with all the medical details of a patient being computationally incorporated and accessible. Molecular science has made many advances in medicine over the last decade, including the Human Genome project, the International HapMap project and genome-wide association research (GWASs). As the key cause of human genetic variability, single nucleotide polymorphisms (SNPs) are now known and are already a valuable resource for mapping complex genetic traits [13]. Thousands of variants of DNA that are associated with diseases and traits have been identified [14]. Personalized medicine can tailor therapies to the particular genotype of the patients by integrating these genetic associations with phenotypes and drug response (Figure 1). While in regular practice today, whole genome sequences are not used, there are still many examples of personalised medicine in current practice [15]. A targeted pharmacogenetic dosing algorithm for warfarin is used for chemotherapy drugs such as trastuzumab and imatinib to treat particular cancers, and the occurrence of adverse effects is minimised by monitoring for susceptible genotypes of drugs such as abacavir, carbamazepine and clozapine [16-21].

Advent of Personalized Medicine

There is actually a paradigm change in the practise of medicine from the predominantly ‘reactive medicine' of the past to a more 'proactive predictive medicine' aimed at disease prevention [22-25]. There is a move towards the care of individual patients rather than treating a disorder, based on a customised, data-driven approach. The convergence of Big Data and Omics revolutions is driving this change. Precision medicine has arisen to functionally interpret omics and big data and promote their application to the provision of healthcare as a technical method. Patients are not separated by illness, or by disease subtype, in this modern age. Alternatively, the objective is to treat each patient as an individual case, integrating a variety of customised details including genomic, epigenetic, environmental, lifestyle and medical history. The hope is that, combined with predictive modelling based on established experiences, the aggregation of these data into an individualised virtual representation of the patient would inform and patient's rational therapy design. In order to achieve these objectives, the objective of precision medicine is to establish computational models that combine clinical and basic science data and information in order to obtain a mechanistic understanding of the disease [26], thereby promoting personalised treatment decisions.

Personalised Medicine Approaches

Precision medicine currently utilises small biomarker panels to achieve some degree of stratification of patients into subgroups of diseases. However a single molecular marker [27], such as the mutation status of a single gene, is still largely stratified in patients. BRAF (V600E) in melanoma [28], MYCN in neuroblastoma [29,30] and the BRCA genes in breast and ovarian cancer are single prognostic gene biomarkers which are used clinically [31-33]. The complexity of cancer and many other human diseases, however, involves omics-scale diagnostics to stratify patients for customised treatments adequately and accurately. Even when omics-scale or biomarker [34] panels are used, treatment decisions are based on a univariate decision rule that does not account for biomarker interactions, let alone integrate or recognise any additional factors that may control the functioning of the biomarker panel (such as omic or environmental data).

As metabolic markers reflect the functional endpoint of physiological pathways and are thus closely linked to the disease phenotype, metabolomics is being explored as a field of great potential for the discovery of novel biomarkers [35]. Metabolomics and the sequencing of circulating microRNAs and cell-free DNA are likely to prove crucial to the ongoing health and disease evaluation by using body fluids to provide a non-invasive way of mapping improvements in disease states [36-39]. Enhanced disease profiling and monitoring should be provided by a step away from relying solely on static mutational data and towards dynamic-omic profiling using technologies such as metabolomics and RNA-seq to produce usable read-outs. Patients can be divided into care classes in the near future by not only assessing their genetic variations, but also by using omic data as an output of the activation status of the disease network.

Future-The Road Ahead

We will continue to see an increase in studies of various forms of "omic". The most prominent field of focus to date has by far been genomics. As technologies evolve, the identification of biomarkers in proteomics, metabolomics, and other as-yet-unnamed "omic" modalities will continue to be seen. Increasingly integrated research can also be seen, taking a system approach to human biology where system biology has concentrated on model organisms to date, mostly single cellular ones, in which the system can be disrupted methodologically and ethically. The coming decade will see more research and insights into mental health conditions centred on biomarkers. To date, cancer and cardiology have gained, to great gain, tremendous publicity. But by contrast, these disease areas are relatively easy to recognise, differentiate, and even measure. For neurologic and psychological disorders, this is not the case. Mental health is a field in which diagnosis and more broadly, phenotyping is as much art as science. It is an area which poses enormous societal burdens, both financially and in terms of quality of life, and is also suitable for a deeper, more physiologically based understanding [40]. Even if therapy is still a long way off, it would be a great leap to have some clear, quantifiable biomarkers from which we might categorise disorders such as depression, bi-polar disorder, and manic-depressive tendencies.

Conclusion

In total, in data-driven health care, we are entering a new age. Bioinformatics approaches continue to make a real difference in the lives of patients. Some of the technical advancements need to catch up with infrastructure, information technology, policy, and culture. Opportunities abound for researchers working at the cutting edge of translational bioinformatics, and the future looks promising.

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