New high-throughput technologies of post genome era: benefits and ethical issues

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ABSTRACT: The fields of molecular cell biology and human genetics have recently experienced several revolutions that have brought new knowledge and new technologies. Large scale sequencing and global functional characterization studies allow simultaneously monitoring thousands of sequences and molecules, thus generating a large amount of data giving a real-time molecular details snapshot of an individual. In this review we briefly refer to some of these novel techniques, including next-generation sequencing methods and CRISPR/Cas9 editing gene systems. The major applications and implications of these novel technologies in research and molecular diagnostics are presented. Ethical issues raised by the implementation of these methods in healthcare systems in the near future are discussed.

Keywords: Human genome; Next-generation sequencing; Genome editing; Ethical issues

Metodologias emergentes de larga escala na era pós-genómica: benefícios e questões éticas

RESUMO: As áreas da biologia celular e molecular e da genética humana sofreram recentemente uma grande revolução que trouxe novo conhecimento e novas tecnologias. Os estudos de sequenciação em larga escala e de caracterização funcional permitem a monitorização simultânea de milhares de sequências e moléculas, gerando uma grande quantidade de dados e fornecendo detalhes moleculares em tempo real e de modo instantâneo de um indivíduo. Nesta revisão faz-se uma referência breve a algumas destas novas técnicas, incluindo os métodos de sequenciação de next-generation e os métodos de edição de genes baseados no sistema CRISPR/Cas9. São apresentadas as potenciais aplicações e implicações destas novas tecnologias nas áreas de investigação e diagnóstico molecular. São também discutidas as questões éticas levantadas pela implementação destas metodologias num futuro próximo.

Palavras-chave: Genoma humano; Sequenciação em larga escala; Edição do genoma; Ética

Introduction

Technical advances in the last decade in molecular cell biology and human genetics created the possibility to analyse samples on a systems level. Therefore, over the past few decades the use of the 'omics' suffix has become familiar especially when the human genome sequence was completed in the early 2000s. It rapidly expanded beyond use for genomics and proteomics to other areas, and terms like transcriptomics, metabolomics, epigenomics, interactomics and pharmacogenomics started to flood the scientific works. In fact, this was the consequence of being possible to use 'omics'-based approaches not only to current but also to emerging research fields. The possibility to 'have global pictures' of an individual in a short period of time in opposition to look, for example, at a single gene or a few components of a cell signalling pathway of an individual, changed the way of doing research (*cf.* Figure 1). 'Omics' approaches accept that a complex system can be better understood if considered as a whole. While more traditional approaches are largely hypothesis-driven, the 'omics' experiments are essentially hypothesis-generating. In this case, holistic approaches are used without a predefined hypothesis, but all data are acquired and analysed to define a hypothesis that can be further tested. The two approaches are not mutually exclusive but instead are complementary[1].

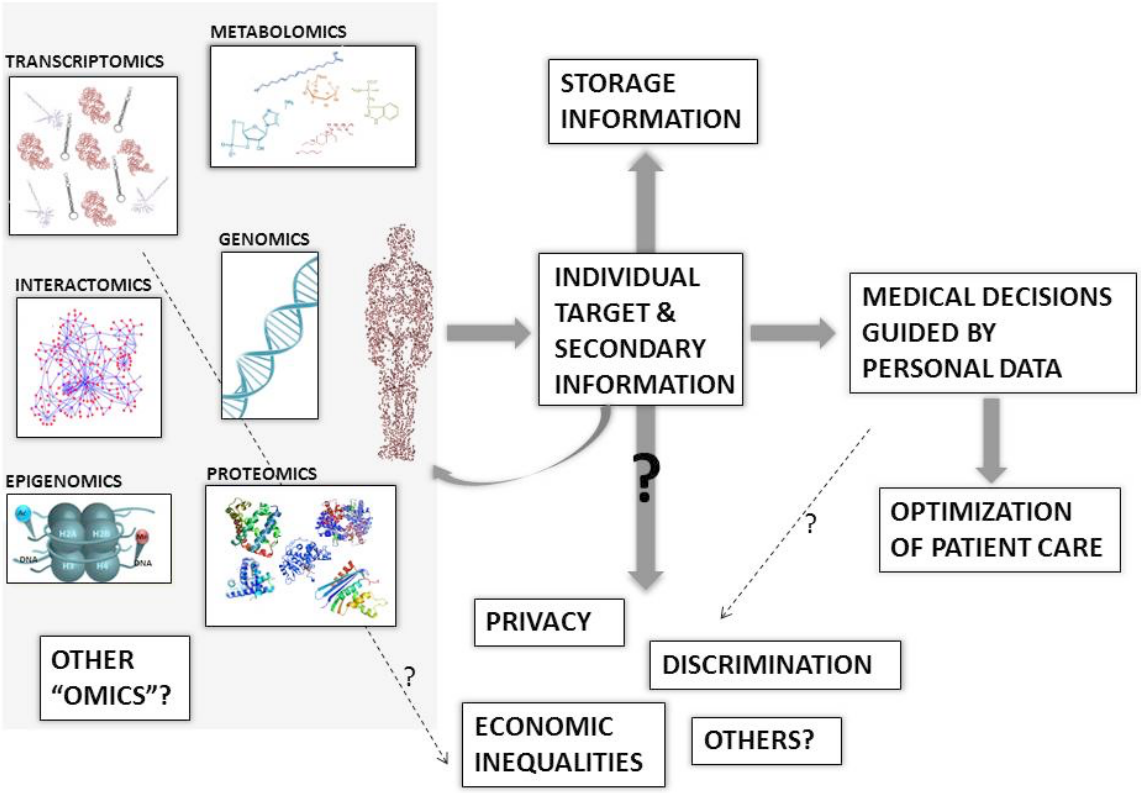

Figure 1. Simplified scheme of 'Omics' impact in human health care and ethical issues.
In the post-genomic era, the "physiology and anatomy" of the human genome i.e., its functionality, has been exploited by large-scale approaches, from genomics to transcriptomics and epigenomics and from proteomics to metabolomics and interactomics. The generated information has been of great value in biomedical sciences, namely for a more precise diagnosis and therapeutics towards individual characteristics. However, the secondary information generated can raise several issues, including ethical ones that need to be carefully addressed.

The implications of these new approaches to the field of biomedical sciences opened incredible new possibilities to understand the molecular mechanisms underlying human diseases and therefore to envisage new strategies of diagnosis, prognosis and therapy. Moreover, the ability to study biological phenomena at 'omics' levels lead to a new paradigm in healthcare by shifting the idea of conventional medicine from 'one-size-fits-all' approach to one based in individual characteristics – Precision medicine. In conventional medicine disease treatment and prevention strategies are developed for the average person, with little consideration for the differences between individuals. Thus, according to the National Institutes of Health (NIH, USA) (https://ghr.nlm.nih.gov/) precision medicine is an "emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person". This new approach will predict more accurately which treatment and prevention strategies for a disease will work better in which groups of people.

In this review we will briefly describe some of the major technological advances in biology and refer to their impact in the biomedical field. We will subsequently refer to the new ethical challenges posed by them.

Novel technologies that allow exploring and editing the human genome

A variety of molecular technologies have been developed in this century paving the way to bioscience and medical advancements and providing new avenues for scientific research.

Next generation sequencing (NGS), massively parallel or deep sequencing is related terms that describe a DNA sequencing technology, which has revolutionized genomic research. In contrast to the previous Sanger sequencing technology, used to decipher the human genome, which required over a decade to deliver the final draft in 2001[2-3], using NGS, an entire human genome can be sequenced within a single day.

Within the genomic analysis performed by NGS, it is possible to study inherited variation or somatic mutations by whole-genome sequencing (WGS) or whole-exome sequencing (WES). In whole-genome sequencing, somatic mutations, including, single nucleotide polymorphisms or insertion-deletion mutations are identified by sequencing the entire genome. This approach has been used to identify several somatic mutations in cancers[4]. The whole-exome sequencing is used to analyse a specific targeted subset within the protein-coding sequences, the exons. In the clinic,

whole-exome sequencing has been increasingly used to assign patients with an unclear diagnosis to a known disease, usually, Mendelian monogenic diseases[5].

Importantly, one of the earliest applications of NGS was to create 'epigenomic maps', showing the location of specific DNA modifications, chromatin modifications and protein--binding events across the human genome. The sites of DNA methylation can be found by sequencing DNA in which the methylated cytosines have been chemically modified (methyl-seq)[6], whereas chromatin (histone) modifications and protein binding to target DNA sequences (e.g., transcription factor binding to gene promoters) can be mapped by chromatin immunoprecipitation-sequencing (ChiP-Seq)[7-8].

Sequencing is also being extensively applied to RNA transcripts (RNA-seq) to determine their abundance, identity or detect novel splice forms, thus contributing to transcriptome analysis[9]. RNA-seq is mainly used for sequencing mRNAs or long noncoding RNAs (lncRNAs). A more recent variant of transcript analysis, miRNA-seq, has been applied to the specific detection and quantification of small non-coding microRNAs. These regulate gene expression by targeting mRNAs for translational repression, degradation, or both that have emerged as important modulators in cellular pathways, such as growth and proliferation, apoptosis, and developmental timing[10].

Both RNA-seq and miRNA-seq have been used for studying gene expression patterns unique to certain cancers and, in the case of miRNA, in cardiovascular diseases, enabling researchers to identify clinically relevant novel biomarkers for specific types of cancer and predictors of cardiovascular diseases[11-14].

In addition to the extensive genome 'anatomy and physiology' provided by 'omics' methods, genomes have also been subject to engineering. The so-called 'molecular scissors' that allow targeted changes to genomes of living cells have evolved along time and are recently based on the system (CRISPR – clustered regularly interspaced palindromic repeats)/CRISPR-associated 9 nuclease (Cas9) (CRISPR/Cas9)[15]. In a simplified way, by delivering the Cas9 nuclease complexed with a synthetic guide RNA (gRNA) into a cell, the cell's genome can be cut at a desired location, allowing existing genes to be removed and/or new ones added[16]. This new genome editing tool has many potential applications in medicine, namely at the field of gene therapy but also raises some important ethical issues, which are further discussed below.

Impact of large-scale sequencing and genome editing in biomedical sciences

The genome-wide based methods have an enormous potential on biomedicine. Some of the most relevant outcomes of these methods are briefly described in this section.

With the emergence of NGS methods, a major advance was carried out in what refers to characterization of genomic variation. Indeed it is now possible for geneticists to assay a very large number of SNPs in an individual. Those genetic variants common enough in populations could be annotated and examined for association with phenotypes and interpreted in clinical settings[17]. The new sequencing technologies should also be able to identify novel genes responsible for undescribed Mendelian disorders in patients with unexplained congenital conditions[18]. Moreover, the comparison of patients and parents genomes will make it possible to spot new mutations. This approach has the potential to be used in prenatal counselling by characterizing germline genomes. Polygenic diseases can also be further characterized through a combination of GWAS (gene wide association studies focused on associations between SNPs) and sequencing. Coupled with functional studies, namely the generation of mouse models, these methods will help characterizing the phenotype of common disorders.

Cancer gene discovery is also being driven by systematic genome-wide efforts, involving the combination of DNA sequencing, copy-number analysis, gene expression analysis and functional studies such as RNA interference. These combined efforts are promoting the grouping of heterogeneous tumours into homogenous sub-groups based on mechanism[19]. The generation of a comprehensive list of all somatic mutations in human cancer cell types will allow defining novel drug targets and generating animal models that will be the basis of novel clinical trials.

The application of genome-wide studies to Immunology will help determining the patterns of B-cell and T-cell receptors in different settings[20], thus making it possible to reconstitute immune repertoires and monitor responses to vaccines or infer disease exposures. Also, microbiomes are starting to be characterized by NGS[21] and further characterisation and association of patterns of microbial communities with diseases processes will be of major clinical interest. Importantly, the impact of microorganisms in human health can also be monitored by assessing their presence in different environments.

Furthermore, NGS can have applications in pharmacogenomics, the ability to predict the response to drugs or their adverse effects in a personalized way, according to the information of each patient's genome as reviewed in[22].

In a different perspective, maps of genetic variation among human populations provided by genomic data will also contribute to unveiling human history and the migration of populations[23], thus reshaping our understanding of the peopling of the globe. It can also contribute to find differences to our closest relatives, such as Neanderthal and chimpanzee. This valuable information can be used to reconstruct several events of human history, from the structure of the ancestral human population in Africa to the subsequent population dispersals and impact of selection (natural or human-mediated) in civilization.

Regarding genome editing, major improvements are still required before molecular scissors, such as the CRISPR/Cas9 platform described above, can be implemented in genomic medicine. Several factors can affect the efficacy of treatment, including the genetic nature of a disease, the required correction, the delivery method and the targeted cells and organs[24]. Nevertheless, this technology has several potential

applications. The targeted gene therapy, mediated by molecular scissors involves manipulation of the genetic material either to delete and replace causal mutations or to induce host mutations that can provide protective functions. Monogenic diseases are thus the most easy to treat this way, since the generation of a dysfunctional copy of the causative gene would reverse the disease state[25]. On the other hand, polygenic diseases, that require simultaneous multiple alterations of the genome are more challenging to treat. The growing knowledge of genomes will allow the complete understanding of the genetic basis of these polygenic diseases, making it possible to subject to multiple genomes editing that will eventually dictate a desired genetic outcome that can reverse the illness. In this context CRISPR/Cas9 system could be used in the treatment of complex diseases such as cancer. Cancer genomes and epigenomes in various cells are very complex, with several SNPs and chromosomal rearrangements. Thus the CRISPR/Cas9 system would be useful, in this case to generate 'next-generation-mouse-models' in which genetic alterations are combined to mimic cancer states[26]. This model would be a valuable tool to validate cancer-related genes identified in The Cancer Genome Atlas. Ultimately, the fact that the CRISPR/Cas9 system was initially discovered as a molecular immunity mechanism against invading pathogens might suggest that it would also be a good system for gene therapy against AIDS or other diseases caused by viral infections, namely those associated with cancers, such as hepatitis virus B and C in liver cancers[27].

Some ethical and social implications: the individual genomic data, privacy and discrimination

In the last years the application of precision medicine approaches to diseases in areas like oncology, psychiatry and cardiovascular conditions started to be a reality. For example in oncology a number of diagnostic tests have already been established as clinical prognostic factors (such as gene expression profiling assays for breast and colorectal cancer and the long-QT syndrome panel) and targeted therapeutics (e.g., trastuzumab and irinotecan)[28]. Therefore, we are gradually observing the precision medicine movement entering clinical settings. In addition to these significant advances and increasing potentialities we should be aware that this will also be accompanied by ethical, legal and social implications. The large amount of data generated by genome-wide approaches creates new challenges to the way how this data are generated, collected, analysed and stored. This process may raise issues related to privacy and discrimination. In fact, if private health information is inappropriately disclosed this could lead to individual discrimination and stigma. This may also affect the individual confidence relationship with physician and other healthcare providers, which may lead to altered behaviours as hiding critical information which will affect the treatment. There is also the risk of these problems becoming a public health threat, e.g. if the individual has an infectious disease or mental illness[29].

Another ethical problem related to the data is the fact that new sequencing technologies, generate additional information This raises the ethical issue of what should be done with WES and WGS "secondary" findings (e.g., carrier status for recessive diseases, cancer predisposition mutations, early-onset disease and late-onset disease, etc.) and if they should be or not communicated to the patient. An interesting discussion of this problem was conducted by Hallowell and coworkers[30], concluding that the process requires full transparency of the purpose of the sample to be collected. Clear protocols for data transfer between research and clinical contexts and accurate information to the patients are also required. Patients should be aware that secondary information may be generated and which are the options of posterior action in the clinical context.

Furthermore the new 'omics' approaches have the potential to go further in finding differences between individuals, opening a new avenue to 'genetic discrimination' in employment, insurance, mortgages or other activities, because they can easily correlate 'differences' with putative economic losses (for discussion see[31]). For example, genomic data can inform if an individual has the susceptibility to develop a certain disease and if this individual belongs to a genetic group that will not be successfully treated with standard medications, therefore representing an increased morbidity, mortality risk and higher health costs. Moreover, the genome has essential features that allow identification (e.g., forensics) and the potentiality to exposure family relationships, which will affect not only the individual but other relatives. Also, direct-to-consumer DNA testing increases the probability that genome data will be made available on the internet and for-profit companies, that can be both considered less regulated environments.

In conclusion we can envisage that in a near future genome sequencing will become a routine practice, which will have a profound impact in medicine, with fast widespread usage of genomic information by health care systems. The maintenance of data confidentiality and individual privacy should be a central concern even before this system is established. However, we are far from being prepared to deal with these issues, as recently demonstrated by the establishment of an NIH working group to manage access to HeLa cell genomic data[32]. Our present limitations to assure the privacy of participants in genomics studies have been reported and discussed in a few recent papers[33-34].

Our challenge is therefore to simultaneously guarantee the security and privacy of genomic data, without significantly compromising its use in research and health care (*cf.* Figure 1). These will require clear policies and legislation to protect individual data and the simultaneous commitment of the computer sciences in cross-talk with geneticists and health care providers to develop efficient and secure bioinformatics techniques to deal and store big genomic data.

Social and economic inequalities, transmitted to subsequent generations, result in the indefensible persistence of health inequalities[35]

The possibility to implement precision medicine in healthcare services has raised the discussion of weather this

new approach will contribute to the elimination of health disparities or instead to accentuate inequalities. Tailoring medical treatment decisions to an individual's genetic profile is thought to decrease costs resulting from ineffective treatments and medicines. In the precision medicine approach an important component of health-care delivery is disease prevention. This requires risk assessment relying in individual genetic information, the use of biomarkers and additional information like family history of a given disease, life style, age, etc. In publically funded health-care systems, the use of risk assessment may allow establishing thresholds that will be used to decide who is going to have access to a given treatment or to an additional screening. At first glance this approach seems to contribute to lower the health costs and a better distribution of limited resources but may have a perverse effect denying excluded individuals to also access accurate health care.

Precision medicine may create or accentuate disparities in the near future related to costs of new healthcare technologies implementation that will not be available for all the individuals at the beginning (*cf.* Figure 1). Brothers et al.[29] discuss that although this in general occurs when new technologies are introduced, it is possible that in the case of countries that have national healthcare services these new approaches may be slowly embraced. In fact, the healthcare systems generally limit coverage to treatments with well-established efficacy. Thus, it is likely that new precision medicine technologies will be first available at private health institutions making it only accessible to small groups of the population that are able to afford them. Based on this scenario some authors support that the ethical ways of using emerging genomics knowledge, namely in pharmacogenetics, would be to carefully define genetic differences between populations instead of strengthening an individualistic 'boutique-style' model of healthcare[36].

Finally the new health paradigms may originate health disparities in society and between distinct populations through the establishment of completely computerized health care services. It is already a reality that individual health records are instantaneously available to different health services and patients may receive their clinical test results by email. In a near future, individuals will be encouraged to have a more active participation in their health care by monitoring their health status, as well as by adjusting treatments to their daily requirements. This requires that patients have access to information technologies and know how to work with it. Therefore a patient can only benefit from this if he/she has access to internet services and an internet capable device, as well as the necessary computer literacy. On the other hand, these new realities may be advantageous for health services in most remote areas by the easily delivery of knowledge and techniques. Thus the scenario is complex and implementation should be thoroughly analysed and adjusted to the population needs and specificities.

Concluding remarks

New high-throughput 'omics techniques are providing exciting opportunities in clinical medicine but present new ethical challenges and are changing the traditional relationships between patients and health care professionals and services. This will require not only that patients will be able to understand the new provided information but also that medical doctors and other healthcare providers will need to know more about molecular genetics and biochemistry[35]. They will increasingly face the need to interpret the results of genetic tests, understand how that information is relevant to treatment or prevention approaches, and convey this knowledge to patients.

The ability to modify genomes of living organisms at precise locations in more specific ways is now a reality by using techniques such as CRISPR-Cas9. This raises effective possibilities to gene therapy at low costs. However this powerful technology would create major ethical concerns if it were used to edit germline genome that change gene(s) beyond a single generation impacting humans and environment. This has lead the European Group on Ethics in Science and New Technologies to release a statement in 2016 on gene editing asking for a broad public debate in this subject[37].

Finally, although this is not the focus of our review, we want to conclude that in the post-genome era the research process is also facing new ethical challenges. This subject is excellently reviewed and analyzed by Vähäkangas[38] who ends the review with a remarkable text that we cannot fail to cite as professors and scientists: Individual scientists, scientific journals, universities and research institutions, as well as society at large, have an essential role in keeping science independent, transparent and self-correcting. Not only fraud, but also carelessness, poor validation, and poor quality control of methods and data violate good scientific practice. We, the senior scientists and the institutions we lead and manage, are responsible for the transfer of research tradition to the next generation of scientists through education, mentorship and setting an example by our own behavior, as well as by creating systems that support good research ethics.

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