Human Genome Project, Personalised Medicine and Future Health Care

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Abstract:	At the turn of the millennium, the Human Genome Project and the upcoming publication of the human genome sequence promised to open an entirely new approach to healthcare, based on the genotype of the individual. This approach was dubbed personalised medicine (PM). However, the analysis of sequencing results revealed that the complexity of the biological world had been underestimated. The major project of revolutionizing medicine through genomics requires a more sophisticated and multilevel understanding of living systems, which in turn demands new data, models and modes of intervention on humans as well as non-human organisms. Thus, the most advanced applications of PM involve a complex interweaving of biological and medical knowledge, as well as increasing attention to the technical systems through which data about any specific individual could be processed. Further, the development of PM needs to include consideration of several key ethical issues, ranging from privacy and data control to the risk that dependence on sophisticated technologies will widen the gap between haves and have-nots both globally and within any one country.

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Human Genome Project, Personalised Medicine and Future Health Care

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Abstract

At the turn of the millennium, the Human Genome Project and the upcoming publication of the human genome sequence promised to open an entirely new approach to healthcare, based on the genotype of the individual. This approach was dubbed personalised medicine (PM). However, the analysis of sequencing results revealed that the complexity of the biological world had been underestimated. The major project of revolutionizing medicine through genomics requires a more sophisticated and multilevel understanding of living systems, which in turn demands new data, models and modes of intervention on humans as well as non-human organisms. Thus, the most advanced applications of PM involve a complex interweaving of biological and medical knowledge, as well as increasing attention to the technical systems through which data about any

specific individual could be processed. Further, the development of PM needs to include consideration of several key ethical issues, ranging from privacy and data control to the risk that dependence on sophisticated technologies will widen the gap between haves and have-nots both globally and within any one country.

Keywords: human genome project; healthcare; personalised medicine; precision medicine; pharmacogenomics; data-intensive science; translational medicine.

Key Concepts

- Personalised medicine describes the direction medical solutions are expected to evolve, towards personalisation and individual tailoring of therapies and treatment regimes that will cut and divide through patient populations. The motor of this promised innovation will be genomic profiling techniques, of nuclear DNA but also ones of latter development such as proteomics, metabolomics, transcriptomics, and so on.

- Biomedicine is an interdisciplinary space involving biological and medical knowledge/expertise as well as IT, where scientific knowledge about biological phenomena is mobilized in order to devise solutions to medical problems**.**

- Data-intensive science describes the mode of scientific research that is emerging as paramount in an age characterised by the increasing reliance and dependence of researchers on the development of complex, distributed infrastructures for data sharing and analysis.

- Postgenomics indicates efforts at creating and understanding models of life and disease that put genomic science and other biosciences at all levels of complexity in relation to each other.

- Translational medicine indicates the fast-developing domain of efforts and debate aimed at improving the translatability of discoveries and techniques from the lab into solutions, drugs and therapies that can be effectively implemented at the point of healthcare delivery.

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Introduction: The Promise of Personalised Medicine (PM)

During the twentieth century, the support received by research in biochemistry and genetics has been unparalleled in the life sciences, eventually culminating in the 3-billion, publicly funded Human Genome Project (Keller, 2000). The unravelling of the human genome sequence promised to open an entirely new approach to healthcare, which would be grounded on the genotype of the individual and thus beget the era of Personalised Medicine (PM) (Collins, 2010, Hood & Friend 2011). Indeed, the last decades have seen incremental successes of linkage analysis and positional cloning. The development of medical genetics has brought progress in unravelling the etiology of major genetic diseases (e.g. Duchenne muscular dystrophy, cystic fibrosis, Huntington disease, myotonic dystrophy, X-linked mental retardation) and hereditary cancer syndromes (e.g. retinoblastoma, neurofibromatosis, and colon, skin and breast cancer). Also, the genome project has stimulated the development of advanced technology to characterize DNA and study genes. Several initiatives for the development of infrastructures for genomic data sharing have been born since, to allow exchange of empirical data but also facilitate analysis of clinical situations (Merelli, Perez-Sanchez, Gesing, & D'Agostino, 2014; Ray, 2015; Staes et al., 2009; Wang & Krishnan, 2014). A crucial spinoff of these activities has been the development and routinization of specific and reliable diagnostic tests, which in a (relatively limited) number of cases have considerably shortened the process it takes to come to a reliable diagnosis (Eisenstein, 2014; Keating & Cambrosio, 2013; Khoury, Evans, & Burke, 2010).

Challenges Ahead

Due to these developments, PM continues to attract major research funding and media attention, and yet the expectations raised by the promise of targeted, individualised treatments are far from being fulfilled (Keating & Cambrosio, 2013; Khoury et al., 2010; Laksman & Detsky, 2011; Longo, 2012). This is largely due to the complexity of building therapeutic

interventions in the absence of a robust, integrated understanding of biological systems and their relation to their environment. Indeed, the difficulties encountered in the quest to treat disease with the help of genetics have revealed that a vast multiplicity of biological entities, structures, levels of organization and their interactions with the environment need to be understood, so as to be able to fully exploit genomic techniques within healthcare (Hedgecoe, 2004; Wistuba et al, 2011; O'Malley & Stotz, 2011). Continuing efforts in genomic research have also yielded widespread recognition of the need for integration with other domains of biomedical inquiry and a broader view over what phenomena are relevant to explaining and intervening on life, and organismic development and evolution (Stevens & Richardson, 2015). More advanced applications of PM thus involve a complex interweaving of biological and medical knowledge, as well as increasing attention to the technical systems through which data about any specific individual could be processed – a shift in the expertise required to develop medical interventions which has strong repercussions for the ways in which medical research is supported, disseminated, managed and translated into therapies. Further, PM requires the development of an industry of consumer genomic services, whose cultural and social consequences need to be assessed and which raises serious ethical questions ranging from privacy and data control (Lunshof, Church, & Prainsack, 2014) and the impact of genomic risk-based information (Green et al., 2013; Laksman & Detsky, 2011; Lyon, 2012), to the risk that dependence on sophisticated medical technologies will widen the gap between haves and have-nots both globally and within any one country.

Model Systems, Functional Genomics and Epigenetics

While often reviled as boring routine by the classical cell and molecular biologist favouring detailed functional study, the isolation of disease genes required original strategies and resourceful tinkering, large-scale collaboration and competition, the development of massive data analysis and sharing infrastructures, and data-intensive analysis and interpretation across several model systems (Leonelli & Ankeny, 2012; Makałowski et al., 2014; Smith & Porter, 2014). The study of human genetic disease and non-

human organisms has highlighted the existence of many novel genetic mechanisms, the impact of which could never have been conceived otherwise. These advances have yielded a better understanding of the chain of events connecting the molecular defects in genes, via the functional disturbances in cells and organs, to the clinical effects on the organism as a whole. This so-called 'genotype–phenotype correlation' is important not only in optimal patient and family counselling, but also to define proper groups for the evaluation of strategies for therapy and prevention, especially when more experimental, pharmacological and gene therapies come within reach. At the same time, most of the processes determining the genotype–phenotype correlation are still elusive, as they depend on complex interactions between multiple genes, different variant alleles of these genes, the tissues and cellular structures within which genes are expressed, and, last but not least, between genes, gene variants, and the environment – including other organisms upon which human health depends, among which microbes have paramount importance (O'Malley & Dupré, 2005). These biomedical questions are being tackled through of a combination of genomic information with large-scale miniaturization and automation. The increasing power of bioinformatics (databases, image processing and data interoperabilities), nanotechnology (the DNA chip and microfluidics devices) and automation (laboratory robotics) are bringing about an unprecedented scaling-up of information gathering, processing and interpretation. With a cost for genome sequencing now plummeting, the possibility of making sequencing a commonplace routine operation in research and care is increasingly within reach. The systematic description of the data in genome projects of humans and other organisms constitutes the first step in this broader endeavour. The combined results of cross-comparison of the data between different genes of one organism and between the genes and genomes of different organisms, the development of targeted and conditionally switchable animal models for human disease, and the large-scale parallel analysis of gene-expression profiles of tissues in normal versus diseased state and during growth and development has been seen as promise to fundamentally improve our diagnostic capacities. However, attempts to develop therapeutic routes, such as gene therapy and targeted drug

development, have indicated the need for more complex models of animal life and disease that account for emergent organizational structures other than genetic code in its various forms (Keating & Cambrosio, 2013; Laksman & Detsky, 2011; Longo, 2012; Samani, Tomaszewski, & Schunkert, 2010). To continue developing our understanding of life, genomic approaches need to be related to knowledge and research from other domains of biology. This has become evident in the renewed attention garnered by areas such as epigenetics, systems medicine and multiscale modelling (Dupré, 2010a, 2010b; Samani et al., 2010; Wolkenhauer & Green, 2013).

Pharmacogenomics

The aim of the Human Genome Diversity (HGD) Project, a population-based offspring of the Human Genome Project, was the elucidation of the individual variation of genes. An application of this developing understanding attracted a lot of attention from the biotechnology and pharmaceuticals industry. The study of genetic factors governing drug response, a field dubbed 'pharmacogenomics', was widely expected to lead to better targeted pharmacological treatments. Ill-understood differences in efficacy and side effects of medicine between different persons can be based on genetic differences in drug uptake and metabolism (Eisenstein, 2014; Keating & Cambrosio, 2013; Longo, 2012). The discovery of these eventually could unlock major possibilities for more effective, individually tailored medical treatments. A welcome consequence could be a reduction of healthcare cost due to ineffective or even disadvantageous drug treatments, and an improvement in health care effectiveness. However, despite promising first successes in the development of targeted drugs, these have often not been lasting or consistent. Genomics have not translated in a one-stop shop solution for the development of next-generation drugs and therapies, and as a result, the debate about translational medicine has arisen as a major concern. The issues that are connected to this slow coming revolution are of technical (Hicks, Wheeler, Plon, & Kimmel, 2011; Longo, 2012) and epistemological nature (Keating & Cambrosio, 2013; Laksman & Detsky, 2011), as well as ethical (Green et al., 2013). From the technical point of view, even new generation sequencing

techniques are a very complex bundle of operations characterized by technical limitations that shape the quality of the map (see also Makałowski et al., 2014; Smith & Porter, 2014). These limitations, coupled with the sheer amount of data that are generated, have overwhelmed our capacities of selecting, linking and interpreting evidence of variation, and of maintaining standardized knowledge bases in shared databases. Furthermore, the variation in responses to drugs and activation of molecular pathways has been associated to a multiplicity of causal factors, which make diagnostic modelling ever more complex and daunts the translation of these findings to clinical solutions (Keating & Cambrosio, 2013; Samani et al., 2010). These issues undermine expectations that the best successes in targeted therapy development can be replicated on a regular basis.

Sequencing and Data Infrastructures

The mapping of genes on a chromosome-by-chromosome basis is now flanked by whole-genome high-throughput sequencing methods. The working draft of the human genome, announced on 26 June 2000, reported on about 30000 human expressed genes, identified and mapped with great precision to specific subregional locations. For the high-quality finishing stage of whole-genome sequencing, a debate developed on how to best perform the quality control and functional annotation of these genes. The 'first-pass' automated global annotation round, completed in April 2003, was followed by several rounds of assessment of the mapping quality, which were supported by the genome database GDB. The importance of GDB in this process exemplifies how the availability of well-curated, comprehensive phenotype-oriented mapping and annotation databases, providing not only gene maps but mapping and application data for clinical research, is crucial to the fruitful translation of genome knowledge into practical applications. Indeed, data infrastructure initiatives have flourished over the last decade, encompassing a wide spectrum of genomic data-based services, from general repositories to support for the analysis of individual cases (Bin Han Ong, 2015; Merelli et al., 2014; Staes et al., 2009; Wang & Krishnan, 2014). At the same time, the demise of GDB in 2008 highlights how databases and related infrastructures have unclear

sustainability and longevity, as their operational costs are not shared across the community in a proportioned way and their adoption is not unanimous (Ribes & Bowker, 2009; Ure et al., 2009; Bastow & Leonelli, 2010).

Intellectual Property

In the wake of the rapid advances in discovering new genes, a fierce debate emerged on public-versus-private aspects of our genome heritage. Especially in the field of the analysis of human cDNA/gene sequences and their comparison with other species to unravel function, major issues are still unresolved on how to strike the balance between, on the one hand, maximal scientific progress and public benefit – typically served by immediate public access of newly generated data – and, on the other, proper patent protection of intellectual property of inventions, required to safeguard the staggering investments to develop therapies. The existence of an independent international organization like the Human Genome Organization (HUGO) founded in 1989, which did not report directly to specific governments, industries or funding bodies, was an important asset to an unbiased international discussion. In 1992, 1996, 1997 and 2000, HUGO has generated policy papers on public access, patenting and related intellectual property issues including single-nucleotide polymorphisms (SNPs) and the effect of the European Directive on patenting biological materials (see Web Links).

Genetic Services and Consumer Genomics

Converting potential genetic services into beneficial healthcare involves tackling several challenges. First, the provision of requested information, which may be very burdensome to the applicant, needs to be properly embedded in expert clinical–genetic healthcare and preceded as well as guided by well-designed, understandable information. This requires additional research into the impact of genetic information and expansion of the professional field. Plans to implement screening programs for major genetic diseases, to widen the access of the public to voluntary preventive and therapeutic options, including lifestyle choices, increase the need to address politically the level of professional care provision. There is an

acute need for training health care professionals at all levels on how to understand genomic information, make it part of professional practice and guide its interpretation by the general public (Samani et al., 2010). And yet, these hoped for developments are connected to, and depend on, the translation of laboratory innovations into new solutions that effectively make a difference for the patients. Furthermore, the public needs to be better supported in discerning the value, impact and limitations of genetic services. A matter of concern has been the proliferation of consumer genomics services, which profile a patient for risk factors of several diseases at once and reconstruct one's genetic makeup, at a fraction of the cost of clinical-level alternatives. It is not clear how such information will impact on an individual's life choices (Wyatt, Harris, Adams, & Kelly, 2013), at a time when one's health is increasingly framed in terms of risk factors (Novas & Rose, 2001), and associated to prevention lifestyle options (Lucivero & Prainsack, 2015). Moreover, a narrative that frames the investigation of an individual's genetic makeup as the reconstruction of one's ancestry relies on a reductive concept of the determinants of individual identity (Dupré 2010a). There are also concerns around whether these services rely on recognized sequencing interpretations and functional gene variants, and the reliability of the sequencing methods used.

Global Ethics

An equally important question is whether society as a whole is ready to assimilate these changes and the associated threats of privacy infringements, unequal access to healthcare and selective inclusion or exclusion from insurance or labour opportunities. Human genetics research and personalized medicine have gained traction in part due to the expectation of accessible solutions to major health problems tailored to the genetic make-up of the individual. Tests are becoming increasingly affordable, and yet not only genomics-based discovery (Ashley et al., 2010; Lupski et al., 2010) diagnostics and therapeutics often relies on the consultation of expert panels to analyse ever more complex patient profiles and discuss best treatment options for a patient – clearly not something that everybody can afford in the same terms. Genetic counselling will be

necessary also for understanding the different degrees of reliability of the tests (and the linked risk of unnecessary therapeutic harm in the case of false positives) and the increasing number of risk factors being identified (Laksman & Detsky, 2011). As a result of differences in the assistance available in deciphering patient profiles, personalized medicine and health-care might become increasingly unequal. Ethical questions also surround the conditions for handling and disclosing incidental findings that might occur as a result of genomic testing of a broad number of variables (Green et al., 2013) in the clinic but also as a result of scientific research (Lyon, 2012). Genomic data can be very durable and predictive of individual profiles, and the increasing number of applications outside healthcare that are going to rely on this data, from ancestry services to policing through DNA phenotyping (e.g. Cookson, 2015) make the eventual function creep particularly concerning. Who is going to decide who is going to benefit from a genome sequencing service, under what conditions, and what health-care and counselling should accompany the procedure? But also, who should have access to the data, where should the data stored and what ownership and control should the patients have on their own sequencing data (Lunshof et al., 2014; Samani et al., 2010)? The realization of new healthcare options depends on resolving both the epistemological question of transnational medicine and the ethical and legal concerns relating to the role of genomics science in society. As demonstrated by the ongoing fierce debate on public versus private issues, commercial development in different Western regions and increased awareness of new forms of exploitation of vulnerable populations, it is indispensible to foster international dialogue on how to reap scientific gains on a worldwide scale and how to fight inequality from being reproduced in new forms.

See also

Commercialization of Human Genetic Research, Human Genome Project, Human Genome Project as a Social Enterprise, Bioinformatics, Role of the Human Reference Sequence in Personal Genomics, Use of Personalized Genomic Information and Pharmacogenetics and Pharmacogenomics

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