



Editorial

Cardiovascular precision medicine: Bad news from the front?



André P. Lourenço (MD PhD)^{a,b}, Adelino F. Leite-Moreira (MD PhD)^{a,c,*}

^a Department of Surgery and Physiology, Cardiovascular Research Centre, Faculty of Medicine of the University of Porto, Portugal

^b Department of Anaesthesiology, São João Hospital Centre, Porto, Portugal

^c Department of Cardiothoracic Surgery, São João Hospital Centre, Porto, Portugal

ARTICLE INFO

Article history:

Received 17 March 2017

Accepted 22 March 2017

Medical sciences have always been guided by evolving algorithms tailored to identify and stratify disease as well as to account for individual patient circumstances and adjust management accordingly. All interventions and surgical procedures are individualized. Medical practice has always been personalized and will remain so despite guidelines, carefully controlled clinical trials, evidence-based and protocol-based routines that often suggest a seemingly uniform treatment for specific conditions. Another prominent feature of medical science and practice is pragmatism. All theoretical research considerations and drug and technology developments are judged by their ultimate effects on patient and population health. Cardiovascular disease remains the main cause of death impaired quality of life and healthcare resource consumption in the Western world.^{1,2} In the last 50 years the most important development in medicine in the industrialized world was the decline of cardiovascular disease prevalence and lethality followed by a drop in mortality of some forms of cancer. Underlying this was a holistic prevention, pharmacology and intervention strategy.^{3,4} During the same period, major developments in biology have brought molecular research and genomics to the limelight of biomedical research. Advances stemming from the human genome project and the molecular biology field enabled affordable high-throughput complete gene analysis⁵ at many clinical research centres paving the way for integration of genetic data in medical sciences and patient management even for common prevalent conditions such as cardiovascular disease. This has led to the emergence of a new field dubbed precision medicine, first defined by Francis Collins as “using information about a person’s genetic makeup to tailor strategies for the detection, treatment, or prevention of disease”.⁶ Research in this field has been highly fostered and sponsored worldwide.⁷ Underlying this new revolutionary

field are various strong premises: (i) that genes and information conveyed by DNA are the sole or main heritable components in living organisms, (ii) that genetic diversity is a consequence of random divergence and natural selection from a small founder population and therefore that a limited number of varying alleles that occur at a high frequency may explain the predisposition to disease (the common-disease common-variant hypothesis),⁸ and (iii) that DNA transcription in a few genome regions orchestrates protein synthesis and thus phenotype (Crick’s central Dogma of molecular biology). High expectations have been created for precision medicine, in Collins’ own words “it is hard to imagine that genomic science will not soon reveal the mysteries of hereditary factors in heart disease, cancer, diabetes, mental illness, and a host of other conditions”.⁹ On the other hand while clinicians were desperately seeking for answers in genes the central dogma of molecular biology and Neo-Darwinists’ Modern Synthesis have been progressively deconstructed by molecular biologists themselves. Indeed, extensive research in recent years has shaken the foundations of evolutionary biology and genetics and brought them back to the realm of physiology.^{10,11} Nobel Prize-winner Barbara McClintock placed the genome in an unusual spot as “an organ of the cell”,¹² we now know that transposons are pervasive in the human genome and may have played a crucial role in evolution but many more other examples clearly document that genetic changes are almost always the result of cellular actions on the genome and that the cell should be better viewed as an active agent that reads and writes its genome over time according to clues from the environment in complex adaptive physiological processes,¹³ actually warranting a reappraisal of Lamarck’s work.¹⁰ Recent works also clearly documented heritability of non-genetic elements, not only of organelles such as mitochondria but also of the entire cell content. Cross-species hybrids derived from transferring the nucleus of an oocyte from one species to an enucleated oocyte from another species reveal that there is either arrest in development or a development course that is closer to the enucleated oocyte

* Corresponding author.

E-mail address: amoreira@med.up.pt (A.F. Leite-Moreira).

species thus phenotype is influenced both by DNA and cytoplasmic content.¹⁴ Indeed, transgenerational transmission of both non-genomic maternal and paternal as well as environmental influences through epigenetic mechanisms is highly likely^{15,16} and may have an important role in human health.¹⁷ Finally, it is now also realized that most of the DNA is not junk, that the processes that orchestrate gene transcription, protein coding and post-translational protein modifications are regulated by highly complex intertwined physiological processes¹³ and therefore that the outcome phenotype will also be very hard to predict. Indeed, this also partly explains variable penetrance and why large numbers of potentially pathogenic gene variants can be found in anyone of us.¹⁸ All of the aforementioned partly explain why genome-wide association studies have been able to identify genes and polymorphisms associated with the risk of common cardiovascular diseases, but usually showing minor or negligible relative risk and no ability to improve current traditional risk scores.^{19–23} Geneticists believe that it will be possible to predict genetic risk by increasing sample size of individual studies, combining studies, looking at population isolates and/or focusing on many more genes.^{24,25} Other experts advocate that only integration of multilevel omics (genomics, transcriptomics, proteomics, and other) with extensive clinical, epidemiological and functional phenotype at evolving time points will enable a systems biology view of cardiovascular disease relying on advanced statistical methodologies and big data analysis.^{26–29} The definition of precision medicine has therefore evolved to “treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations” with the ultimate aim of “improving clinical outcomes for individual patients and minimizing unnecessary side effects”.³⁰ This daunting nascent task will warrant large collaborative international platforms to overcome regulatory, ethical, social and economic constraints in order to engage healthy and diseased individuals, practicing healthcare professionals and researchers as contributors to huge knowledge databases where overarching big data from multiple interoperable platforms including electronic health records and omics is uniformly integrated and made available for analysis by experts.³¹ Hopefully bioinformatics will extract valuable and relevant clinical information from these fuzzy logic systems by big data analytics.^{32,33} It is not clear how missing data, unmeasured confounding factors, treatment selection and sample selection biases or other known limitations for observational data will be accounted for by big data analytics. This and other concerns about big data analytics application to health care have been extensively reviewed.²⁸ A recent report showed minor additive value of big data analytics to predict heart failure related hospital readmissions compared with simpler models.³⁴ According to the most optimistic views we are living one of the most profound periods of progress in biology and medicine, experiencing a revolution whereby a global project of data collection, sharing and analysis will lead to evidence-based highly-effective precision medicine therapy and prevention, improved clinician-to-patient communication, improved citizen-centred healthcare and well-being.³⁵ However experience often tells us that optimistic views, wishful thinking and moonshots are not the most profitable and pragmatic.^{36–38} Just as Candide eventually realized after a harsh course through life following his optimistic Leibnizian master Pangloss’s advices that he was better off cultivating his own garden (Voltaire, 1759), so we may come to the conclusion that eventually nothing will replace clinical, epidemiological and physiological research in medical sciences.

Funding acknowledgments

This work was supported by the project DOCnet (NORTE-01-0145-FEDER-000003), supported by Norte Portugal Regional

Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF), the project NETDIAMOND (POCI-01-0145-FEDER-016385), supported by European Structural and Investment Funds, Lisbon’s Regional Operational Program 2020 and national funds from the Portuguese Foundation for Science and Technology.

References

- Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2095–128.
- Brunner-La Rocca HP, Fleischhacker L, Golubnitschaja O, Heemskerck F, Helms T, Hoedemakers T, et al. Challenges in personalised management of chronic diseases – heart failure as prominent example to advance the care process. *EPMA J*. 2015;7:2.
- Cooper R, Cutler J, Desvigne-Nickens P, Fortmann SP, Friedman L, Havlik R, et al. Trends and disparities in coronary heart disease, stroke, and other cardiovascular diseases in the United States: findings of the national conference on cardiovascular disease prevention. *Circulation*. 2000;102:3137–47.
- O’Flaherty M, Buchan I, Capewell S. Contributions of treatment and lifestyle to declining CVD mortality: why have CVD mortality rates declined so much since the 1960s? *Heart*. 2013;99:159–62.
- Hayden EC. Technology: the \$1,000 genome. *Nature*. 2014;507:294–5.
- Collins FS, Green ED, Guttmacher AE, Guyer MS. Institute USNHGR. A vision for the future of genomics research. *Nature*. 2003;422:835–47.
- Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med*. 2015;372:793–5.
- Lander ES. The new genomics: global views of biology. *Science*. 1996;274:536–9.
- Collins FS. Contemplating the end of the beginning. *Genome Res*. 2001;11:641–3.
- Noble D. Physiology is rocking the foundations of evolutionary biology. *Exp Physiol*. 2013;98:1235–43.
- Noble D. Neo-Darwinism, the modern synthesis and selfish genes: are they of use in physiology? *J Physiol*. 2011;589 Pt 5:1007–15.
- McClintock B. The significance of responses of the genome to challenge. *Science*. 1984;226:792–801.
- Shapiro JA. Revisiting the central dogma in the 21st century. *Ann N Y Acad Sci*. 2009;1178:6–28.
- Sun YH, Chen SP, Wang YP, Hu W, Zhu ZY. Cytoplasmic impact on cross-genus cloned fish derived from transgenic common carp (*Cyprinus carpio*) nuclei and goldfish (*Carassius auratus*) enucleated eggs. *Biol Reprod*. 2005;72:510–5.
- Rakyan VK, Chong S, Champ ME, Cuthbert PC, Morgan HD, Luu KV, et al. Transgenerational inheritance of epigenetic states at the murine Axin(Fu) allele occurs after maternal and paternal transmission. *Proc Natl Acad Sci U S A*. 2003;100:2538–43.
- Martos SN, Tang WY, Wang Z. Elusive inheritance: transgenerational effects and epigenetic inheritance in human environmental disease. *Progr Biophys Mol Biol*. 2015;118:44–54.
- Pembrey ME, Bygren LO, Kaati G, Edvinsson S, Northstone K, Sjöström M, et al. Sex-specific, male-line transgenerational responses in humans. *Eur J Hum Genet*. 2006;14:159–66.
- Cassa CA, Tong MY, Jordan DM. Large numbers of genetic variants considered to be pathogenic are common in asymptomatic individuals. *Hum Mutat*. 2013;34:1216–20.
- Ehret GB, Caulfield MJ. Genes for blood pressure: an opportunity to understand hypertension. *Eur Heart J*. 2013;34:951–61.
- Paynter NP, Chasman DI, Paré G, Buring JE, Cook NR, Miletich JP, et al. Association between a literature-based genetic risk score and cardiovascular events in women. *JAMA*. 2010;303:631–7.
- Lieb W, Vasan RS. Genetics of coronary artery disease. *Circulation*. 2013;128:1131–8.
- Olesen MS, Nielsen MW, Haunso S, Svendsen JH. Atrial fibrillation: the role of common and rare genetic variants. *Eur J Hum Genet*. 2014;22:297–306.
- Talmud PJ, Hingorani AD, Cooper JA, Marmot JA, Brunner EJ, Kumari M, et al. Utility of genetic and non-genetic risk factors in prediction of type 2 diabetes: Whitehall II prospective cohort study. *BMJ*. 2010;340.
- Wray NR, Goddard ME, Visscher PM. Prediction of individual genetic risk of complex disease. *Curr Opin Genet Dev*. 2008;18:257–63.
- Palotie A, Widen E, Ripatti S. From genetic discovery to future personalized health research. *New Biotechnol*. 2013;30:291–5.
- Chen R, Mias GI, Li-Pook-Than J, Jiang L, Lam HY, Chen R, et al. Personal omics profiling reveals dynamic molecular and medical phenotypes. *Cell*. 2012;148:1293–307.
- Roukos DH. Networks medicine: from reductionism to evidence of complex dynamic biomolecular interactions. *Pharmacogenomics*. 2011;12:695–8.
- Rumsfeld JS, Joynt KE, Maddox TM. Big data analytics to improve cardiovascular care: promise and challenges. *Nat Rev Cardiol*. 2016;13:350–9.
- Ouzounian M, Lee DS, Gramolini AO, Emili A, Fukuoka M, Liu PP. Predict, prevent and personalize: genomic and proteomic approaches to cardiovascular medicine. *Can J Cardiol*. 2007;Suppl. A:28a–33a.

30. Jameson JL, Longo DL. Precision medicine – personalized, problematic, and promising. *N Engl J Med.* 2015;372:2229–34.
31. Langley GR, Adcock IM, Busquet F, Crofton KM, Csernok E, Giese C, et al. Towards a 21st-century roadmap for biomedical research and drug discovery: consensus report and recommendations. *Drug Discov Today.* 2017;22:327–39.
32. Liu H, Zhang F, Mishra SK, Zhou S, Zheng J. Knowledge-guided fuzzy logic modeling to infer cellular signaling networks from proteomic data. *Scient Rep.* 2016;6:35652.
33. Groeneveld PW, Rumsfeld JS. Can big data fulfill its promise? *Circ Cardiovasc Qual Outcomes.* 2016;9:679–82.
34. Bottle A, Gaudoin R, Goudie R, Jones S, Aylin P. Health Services and Delivery Research. Can valid and practical risk-prediction or casemix adjustment models, including adjustment for comorbidity, be generated from English hospital administrative data (Hospital Episode Statistics)? A national observational study. Southampton (UK): NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK; 2014.
35. Beckmann JS, Lew D. Reconciling evidence-based medicine and precision medicine in the era of big data: challenges and opportunities. *Genome Med.* 2016;8:134.
36. Joyner MJ. Precision medicine, cardiovascular disease and hunting elephants. *Progr Cardiovasc Dis.* 2016;58:651–60.
37. Joyner MJ, Prendergast FG. Chasing Mendel: five questions for personalized medicine. *J Physiol.* 2014;592:2381–8.
38. Janssens AC, van Duijn CM. Genome-based prediction of common diseases: advances and prospects. *Hum Mol Genet.* 2008;17:R166–73.