

# QJM Review: Systems medicine: helping us understand the complexity of disease

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## Summary

Advances in genomics and other -omic fields in the last decade have resulted in unprecedented volumes of complex data now being available. These data can enable physicians to provide their patients with care that is more personalized, predictive, preventive and participatory. The expertise required to manage and understand this data is to be found in fields outside of medical science, thus multidisciplinary collaboration coupled to a systems approach is key to unlocking its potential, with concomitant new ways of working. Systems medicine can build on the successes in the field of systems biology, recognizing the human body as the multidimensional network of networks that it is. While systems medicine can provide a conceptual and theoretical framework, its practical goal is to provide physicians the tools necessary for harnessing the rapid advances in basic biomedical science into their routine clinical arsenal.

## Introduction

The human body and the diseases it develops embody enormous levels of complexity. To manage this complexity, biological and medical science have tended to employ a Cartesian reductionist approach, breaking down complex problems into smaller, simpler and more tractable units. About 160 years ago, Rudolf Virchow, the founder of modern pathology, introduced the concept of cellular pathology,<sup>1</sup> which put medicine on a new theoretical footing by explaining the origin of diseases as a malfunction of cells. This 'divide and conquer' method has provided an efficient intellectual framework and rational tools which spurred on biomedical research to the zenith of the achievements that have coined modern medicine in the 20th century. However, we now start to feel the headaches in the aftermath of this success. Medicine is fragmenting into ever more specialized disciplines, and the rapid progress in basic science challenges seems to outpace its fruitful conversion into useful tools for medical practice.<sup>2</sup> Is there a new paradigm that can mend this gap?

Life science has born the new field of systems biology that aims to study the broader biological 'system' in a more holistic way, instead of focusing on single molecules.<sup>2</sup> By using mathematical modelling and high-throughput tools, more complex aspects of biology can be studied. This not only includes the interpretation and integration of largescale data (such as genomic, transcriptomic, proteomic and other -omics data) but also for instance the study of complex features in intracellular communication networks, which often display features that are not obvious to the human mind. Using this approach,

concepts of a wide variety of disciplines such as mathematics, physics and engineering are applied to biological systems.<sup>3</sup> The tools and approaches that are being developed for systems biology have the potential to make a more translational impact in the arena of medical science. This review will consider how 'systems medicine' can aid physicians in handling more complex data in their day-to-day practice. We also will discuss how systems medicine can precipitate a broader shift away from current reactive and reductionist practices towards implementing and embracing a medical science that is personalized, predictive preventive and participatory.<sup>4,5</sup>

## Personalized medicine is taking into account complexity

In the medical practice, especially in that of the general practitioner, a more holistic, systems approach has always been used. The practitioner is confronted with the patient as a whole, and focuses on their individual needs and concerns. Every physician knows that each patient is different, that there is a need for a personalization of the medical treatment that they provide. He or she constantly has to try to integrate data on the emotional state of the patient, different comorbidities, environmental factors, family history, etc. In other words, physicians deal with a lot of non-linear, multidimensional information, while the medical science they need to use to make decisions provides them with tools to make linear, reductionist decisions. There is an overall theme of 'one disease, one risk factor, one target' with a lack of dynamic information. In the coming decade, systems medicine aims to provide the tools to take into account the complexity of the human body and disease in the everyday medical practice.

## The predictive and preventive power of -omics: genome testing and beyond

The concept of genetic testing for risk factors is widely understood by the general public. For instance, the BRCA gene test for breast and ovarian cancer has received much media attention, and genetic testing for DPYD mutations can help prevent very severe toxicity of the frequently described anticancer drug 5-fluorouracil in patients with malignancies of the gastrointestinal tract.<sup>6</sup> Such tests have evolved from single genes to a more high-throughput approach; for \$99 anyone can now send in a saliva sample get a genetic test for a long list of risk factors,<sup>7</sup> and it is anticipated that within the next years whole-genome sequencing will be a standard test. Although this may seem far away from being implemented in the medical practice, prices of sequencing and other -omic techniques have fallen rapidly over the last decade. In the case of genome sequencing, costs per genome have tumbled from more than \$100M in 2001 to under \$10 000 in 2013 (Figure 1).<sup>8</sup> Human leukocyte antigen typing through deep sequencing for instance is already a lot more cost effective than the standard antigen-based methodologies. Moreover, this also allows for high-throughput screening, making it not only cheaper but also more suitable for comprehensive disease-association studies with large cohorts.<sup>9</sup>

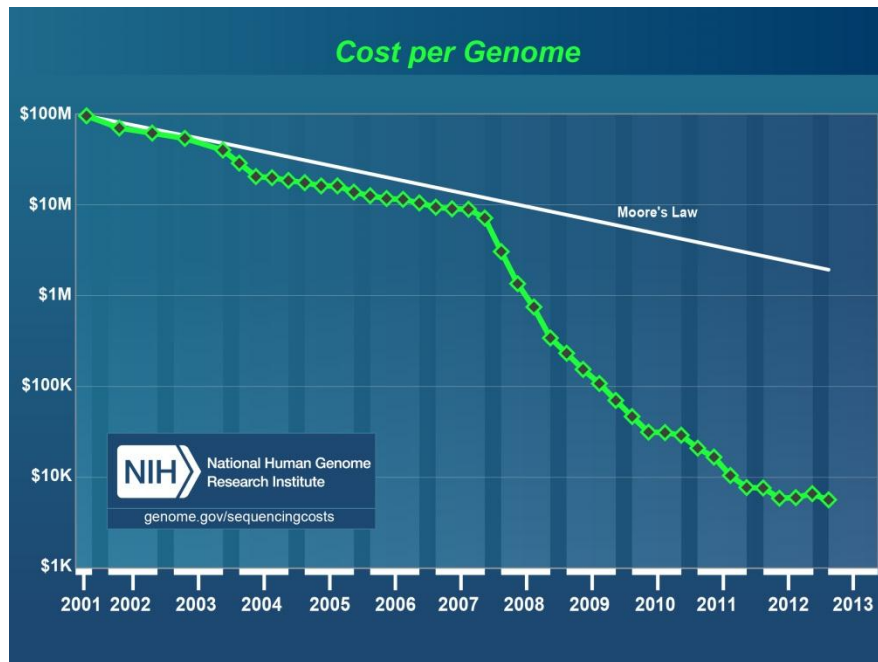


Figure 1. Cost of sequencing per genome compared to 'Moore's law' adapted from Wetterstrand<sup>8</sup>.

The use of a variety of -omics data in the day-today medical practice may still appear a futuristic utopia. However, a recent study using an integrative personal -omics profile (iPOP), an analysis that combines genomic, transcriptomic, proteomic, metabolomics and antibody profiles of blood components, followed a single generally healthy individual for a 14-month period.<sup>10</sup> This research not only illustrated the utility of genomic sequencing for predicting disease risks but it also showed that by monitoring a large number of molecules, the researchers could develop a more comprehensive view on the development of the disease, not only linking it to risk factors but also being able to predict when the risk would manifest itself as disease. They were able to detect the onset of two viral infections and the early onset of type II diabetes. The wealth of information by this longitudinal iPOP analysis revealed unexpected molecular complexity reflecting dynamic changes between healthy and diseased states. Systems approaches to medical science such as this will lead to truly personalized health monitoring and predictive medicine. In addition, substantial efforts are made to bring the necessary tools and instruments from the research laboratory closer to the clinic in a more cost-effective way.<sup>11</sup>

## Systems medicine as a tool for diagnosis, prognosis and therapy

As we have seen, the technologies to get large amounts and different types of data will soon be affordable and readily available in the clinic. But what are we going to do with these long lists of data? Taking all this data into account, and integrating it, is not a trivial task when taking decisions in the daily practice. The sheer volume of data necessitates multidisciplinary interaction; a general practitioner cannot make diagnostic and therapeutic decisions based on hundreds of thousands of data points of -omics data by integrating it in his or her head, they require support of experts from other fields. The development of mathematical and information science tools has opened up possibilities to mine these large sets of data, to post-process them and to reduce the noise in the data. To ensure that data

collected by physicians can be fed back into the health system, a concomitant requirement is the greater standardization of data, enabling colleagues across the UK and Europe to improve the care they provide to their patients from cumulative information collected in every physician's surgery.

There is a need for flexible, integrative systems approaches to combine such -omics data with clinical, societal and environmental factors including sex, type of work, sleep and eat habits, etc.<sup>4</sup> Mathematical models integrating different types of data are already used for optimizing healthcare management. One example of a model that integrates physiology, a list of biological variables, and the major symptoms, tests, treatments and outcomes for diabetes is Archimedes. This model has been used for research of different healthcare aspects, such as the impact of comorbidity on colorectal cancer screening cost effectiveness in diabetic populations.<sup>12</sup>

Systems medicine tools allow the clinician to consider the human body as a complex and multidimensional set of interacting networks at multiple levels of biological organization. The human body is composed of different networks of cells, such as the neuronal network, and within each cell, at the molecular level, there are for instance protein–protein interaction networks, gene regulatory networks, metabolic networks, etc. All these different networks are also very dynamic. Changes in the dynamics of these (sub)networks, or a rewiring, can affect the entire network and result in disease. Research into the effects of these network structures on disease progression will lead to the identification of novel disease genes and pathways. A disease phenotype is rarely a consequence of an abnormality in a single gene or gene product, but rather it is the result of various pathological processes that interact in this complex network. Disease networks can explain the comorbidity of conditions, and offer new ways for early detection and prevention of comorbidities, while this network-based approach can also lead to novel disease classification, on the basis of molecular and environmental factors, in a holistic manner. In this way, these networks can form computing tools to assist in medical decision-making.<sup>4,13–15</sup>

Including new compounds, or marketed drugs in these network structures can offer new, or better, targets for drug development and new prognostic markers. It also offers a cost-effective way to predict adverse effects, and to reposition already approved drugs.<sup>16–18</sup> By repositioning existing drugs, and providing tools for a more evidence-based patient stratification, systems medicine will reduce the costs of health care to society. Systems approaches can also help physicians in rethinking treatment regimens and designing rational, individually tailored multi-drug treatments. Mathematical modelling approaches are currently used in chronotherapy, where the timed administration of a drug is based on the biological rhythms of the patient to optimize efficacy.<sup>19</sup> Designing efficacious drug combinations is another complex matter where mathematical modelling will help. Lee et al.<sup>20</sup> constructed a data-driven mathematical model that was based on the expression levels or activation states of 36 signalling proteins in multiple signalling pathways, and phenotypic cellular responses, upon exposure to the epidermal growth factor receptor (EGFR) inhibitor Erlotinib and the DNA-damaging doxorubicin, both individually and in combination, of triple negative breast cancer cells. They were able to predict and validate that pre-treatment, and not co-treatment or post-treatment, with EGFR inhibitors significantly rewires the signalling network of these cancer cells, and sensitizes them to subsequently applied DNA damaging agents by chemotherapy.

## Needs for implementation: participatory medicine

The new possibilities of systems medicine can only be truly harnessed by a cultural change in the way we collect, share, manage and, fundamentally, how we view medical data. Multidisciplinary collaborations should utilize expertise in information science, computational science and mathematics to ensure that the patient data collected by physicians can readily be assimilated by other physicians and medical researchers. Electronic medical records for instance already form an important source of longitudinal patient records, and could further be complemented with standardized -omics data.<sup>21</sup> The contiguous development of an infrastructure and the necessary social, legal and ethical regulations to enable sharing of data will be a fundamental part of this process, but above all, the cooperation and participation of the patient is paramount. Patients of all socio-economic levels will need to be empowered to make informed decisions regarding their personal medical records, and this will require a process of education for both the patient and the physician, highlighting the personal and societal benefits that come from the sharing of data. To formulate the clinical needs and specific issues systems medicine has to address, the European Commission has funded the Coordinating Action Systems Medicine consortium (CASyM, [www.casym.eu](http://www.casym.eu)) under the Seventh Framework Programme for Research to formulate a roadmap that will guide this European-wide implementation of systems medicine. CASyM aims to be integrative, bringing all stakeholders in this multidisciplinary field together. This includes not only researchers, physicians, pharmaceutical industry and policy makers but also the patient him or herself.

## Conclusions

With the significant advances in -omics data in the last decade, there are opportunities for the wealth of new data now available to make a real difference to treatment that patients receive. However, access to this data will bring with it new challenges and the need for physicians to incorporate new ways of working. Systems medicine will not replace the physician by a computer; rather it will provide the physician with hands-on computational tools to integrate complex patient -omics information, the dynamics of the different networks of the human body, healthcare management and environmental factors. By helping the physician to consider all this information while making diagnostic and therapeutic decisions, a new era of cost effective, preventive, predictive, personalized and participatory medicine is just around the corner.

## Acknowledgements

This work was supported by the Science Foundation Ireland under Grant No. 06/CE/B1129 and by CASyM, Seventh Framework Programme under the Health Cooperation Theme and Grant Agreement # 305033.

Conflict of interest: None declared.

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