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Systems biology: personalized medicine for the future?

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Systems biology is actively transforming the field of modern health care from symptom-based disease diagnosis and treatment to precision medicine in which patients are treated based on their individual characteristics. Development of high-throughput technologies such as high-throughout sequencing and mass spectrometry has enabled scientists and clinicians to examine genomes, transcriptomes, proteomes, metabolomes, and other omics information in unprecedented detail. The combined 'omics' information leads to a global profiling of health and disease, and provides new approaches for personalized health monitoring and preventative medicine. In this article, we review the efforts of systems biology in personalized medicine in the past 2 years, and discuss in detail achievements and concerns, as well as highlights and hurdles for future personalized health care.

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Introduction

The rapid development of high-throughput technologies and systems approaches has greatly advanced the field of personalized medicine, and is shifting the paradigm of future health care from disease diagnosis and treatment to predictive and preventative medicine and personalized health monitoring [1,2]. It is expected that future personalized health care will benefit from the combination of personal genomic information with longitudinal, global monitoring of molecular components that reflect real-time physiological states, as demonstrated in our recent study [3••]. In this article we review the latest progress in the field of systems biology and its impact on personalized medicine, and discuss in detail the benefits and concerns in the application of systems approaches to individualized health care.

Whole genome sequencing in genetic disease research

The revolution of high-throughput sequencing technologies has led to rapid decrease in DNA sequencing cost [4]. As a result, whole genome sequencing (WGS, as well as whole exome sequencing, WES, a targeted version of high-throughput sequencing that focuses on the sequences of protein coding regions) becomes an affordable tool to help understand the genetic basis of health and disease. WGS/WES enables one to obtain digital, single-base resolution genome/exome information from any sample of interest at an affordable price in a short period of time. Analysis of these samples reveals a list of variants that has enabled researchers to examine the genetic basis of diseases with unprecedented details. To date huge amount of data have been generated from whole genomes and/or exomes for both healthy and diseased individuals, and the information not only has helped with disease stratification and mechanism elucidation, but also is transforming people's perspective of future health care from disease diagnosis and treatment to personalized health monitoring and preventative medicine [1,5•].

The field of cancer research has markedly benefited from WGS/WES. Genomes of various cancers are being sequenced through individual or collaborative efforts such as the Cancer Genome Atlas (http://http://cancergenome.nih.gov/) and the International Cancer Genome Consortium (http://http://www.icgc.org/), and the number keeps increasing exponentially. Sequenced cancer genomes include breast cancer [6–8], ovarian cancer [9], small-cell lung cancer [10], melanoma [11], chronic lymphocytic leukemia [12], Sonic-Hedgehog medulloblastoma [13], pediatric glioblastoma [14], and hepatocellular carcinoma [15], just to name a few. In addition to bulk cancer sequencing, single-cell level cancer exomes have also been examined with WES [16,17]. When compared to normal tissues, these efforts identified somatic mutations for the specific cancer genomes as well as molecular markers for cancer subtyping, which may provide potential targets and guides for personalized cancer treatment. In addition to sequencing cancer genomes, WGS also helps identify spontaneous mutations in the 'normal' genome of cancer patients that may lead to carcinogenesis. For example, Link *et al.* identified a novel, germline *de novo* p53 deletion in a female patient who developed 3 different types of cancer in a short period of 5 years [18].

In addition to the analysis of cancer samples, whole genome information also helped with causal gene identification for other diseases and complications at the personalized level. Bainbridge *et al.* sequenced the complete genomes of a fraternal twin pair and identified a pair of compound heterozygous mutations in the *SPR* gene

responsible for the dopa (3,4-dihydroxyphenylalanine)-responsive dystonia in both twins. They were able to improve the health of the children by supplementing the L-dopa therapy with 5-hydroxytryptophan, the serotonin precursor whose synthesis depends on SPR activity [19••]. Roach *et al.* investigated the power of WGS in a family quartet in which both children had two recessive disorders – Miller syndrome and primary ciliary dyskinesia [20••]. The authors demonstrated an elegant example of rare disease causal gene identification with WGS in just one core family of four. This approach was further improved by Dewey *et al.*, who identified multiple high-risk genes in a family quartet with history of familial thrombophilia, obesity and psoriasis [21••]. By implementing the method of Roach *et al.* with a major allele reference sequence, Dewey *et al.* managed to identify 94% of genotyping errors.

Personalized disease risk estimation and health monitoring with integrative omics

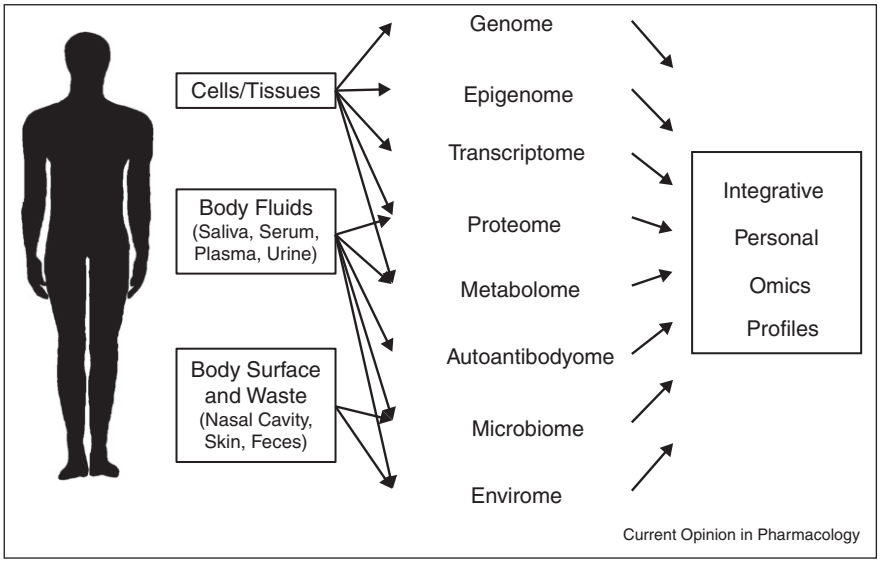
The power of systems biology in personalized medicine lies not only in disease mechanism elucidation, but also, more importantly, in disease risk estimation, personalized health monitoring and preventative medicine. Most disease complications are easier to be reversed when they are still at their early stages. Systems biology provides powerful tools to monitor molecular profiles and detect subtle changes that may indicate biological network perturbation. Physicians and pathologists are actively incorporating systems means to achieve molecular disease diagnosis [22,23].

Genomic sequence has the potential to convey valuable information on disease risks and drug response efficiency. Ashley *et al.* analyzed the genome of a patient [24] with a family history of vascular disease and early sudden death but no clinically significant medical record, and identified elevated post-test probability risks including myocardial infarction and coronary artery disease [25•]. The authors found rare variants in 3 genes associated with sudden cardiac death and one with coronary artery disease, as well as 69 variants that may affect drug response in the patient's genome. The authors proposed that knowing the information of the genetic risks and pharmacogenomic variants may be important for future personalized medical care of this specific patient.

However, genomic information may not always be sufficient to predict a person's health, as other factors such as environmental contributions and/or event triggers might also be important for actual disease development [26]. Roberts *et al.* estimated the predictive capacity of whole genome information by modeling the risk of 24 diseases in a large number of monozygotic twins [27•]. They estimated the distribution of genotypes that best fitted the observed concordance/discordance of any disease for the monozygotic twins. The authors observed that for most diseases, the relative risk for most of the tested individuals would not differ significantly from that of the population, and only $\geq$1 disease(s) could be alerted for any specific individual in the best case scenario. The authors concluded that WGS were of limited value for predicting disease outcome. Since disease outcome is probabilistic and any given individual is at risk for multiple diseases (as well as high penetrance Mendelian diseases not covered in the study), their result is not surprising. The realistic view is that a genome sequence suggests increased risk for multiple diseases that should each be monitored, as the specific individual with the genome will have an elevated chance of obtaining any one of these diseases. As another example, Baranzini *et al.* failed to find evident genomic, epigenomic or transcriptomic differences in monozygotic twin pairs discordant in multiple sclerosis, despite the fact that genetic components had long been implicated [28•], thus it is likely that environmental factors also contribute significantly to this disease.

As transcriptomic, proteomic and metabolomic information are better reflectors of phenotypes than genomic sequences alone, combining genomic information with longitudinal monitoring of these omics should enable researchers to obtain real-time information of a person's physiological status. Owing to the circulatory nature of blood through various parts of the human body, we believe that comprehensive measurement of multiple blood components will be particularly valuable for monitoring physiological health states of a person. To achieve this, we performed a study on a generally healthy volunteer with integrative Personal Omics Profile (iPOP) analysis during a 14-month period [3••]. In our study, we determined the genome of this individual at high accuracy with 2 WGS (Illumina and Complete Genomics) and 3 WES (Agilent, Roche Nimblegen and Illumina) platforms, and identified genetic predispositions for this individual (both for diseases, including Type 2 Diabetes, T2D, and for drug responses). We then successfully monitored personalized physiological state changes that occurred during 2 viral infections and the onset of T2D with integrative information of the transcriptome, proteome and metabolome from blood components (peripheral blood mononuclear cells and serum). In the integrative profile, we observed both trend changes, which may be associated with more gradual changes, and spike changes, in which particular genes and pathways were enriched especially at the beginning of each physiological state change event. The integrative analysis provided a much more comprehensive view of the biological pathways that changed during disease onset. We also observed dynamic changes in allele-specific expression and RNA editing events that might also be associated with the corresponding physiological states. Importantly in this study, because of the genome sequencing and active monitoring, the onset of T2D was detected in its early stage, and its condition was effectively controlled

Figure 1



Integrative Personal Omics Profile (iPOP) analysis. Various types of systems data can be generated and integrated with the iPOP analysis. Note that this approach is highly modular and can be tailored to meet specific needs of different studies.

and reversed in the volunteer by proactive interventions such as diet change and physical exercise. This study therefore serves as a successful proof-of-principle for predictive and preventative medicine with iPOP. We believe our iPOP approach has opened new venues for personalized medicine, which can be readily tailored and applied to monitor any disease or physiological state changes of interest. Our approach is highly modular, as additional omics information (e.g. the methylome, or omic profiles summarized in the next paragraph) and quantifiable environmental factors can be added to our integrative profile, and different combinations of its components can be selected for specific studies [Figure 1].

In addition to the genome, epigenome, transcriptome, proteome and metabolome of the human body, systems profiling of other omics such as the gut microbiome, microRNA profiles and immune receptor repertoire may also be important for health monitoring and personalized medicine, either alone or in combination with other iPOP omics. Gut microbiome has been considered as the 'extended genome', which includes all the symbiotic microorganisms in the human gastrointestinal tract, and is individual-unique [29•]. The gut microbiome may play an important role in drug metabolism. For example, it contributes to the interpersonal variation of the degradation of simvastatin, a commonly used drug for cholesterol control [30]. MicroRNA is another important profile for personalized health monitoring. This layer of post-transcriptional regulation controls various tumor initiation drivers [31], and extracellular microRNA species may serve as biomarkers for various diseases [32]. B-cell and T-cell receptor repertoire are important indicators of the activity of host immune response, and sequencing the pool of unique B-cell and T-cell receptors (termed as repertoire-sequencing, or Rep-Seq by the authors) may give us detailed information on the immune response of the host [33].

In addition, omics profiling is also expected to help us understand complex diseases and processes such as asthma [34], inflammation [35], immune response [36], and traditional Chinese medicine [37].

The power of data re-mining

Deep re-mining of combined publicly available data (e.g. expression, genome-wide association and candidate association data) may also help with the identification of disease-associated genes. By searching for genes that appeared multiple times in 130 functional microarray experiments, Butte and co-workers identified CD44 as the top candidate associated with T2D [38]. The group also found that T2D risk alleles exhibited significant bias in human populations by curating data from 5065 scientific articles, with the genetic risk highest in Africans and lowest in East Asians [39].

Concerns with systems biology-powered personalized medicine

As reviewed above, omics approaches are reshaping health care towards personalized health monitoring and personalized medicine, and our vision is shared with a growing number of scientists, physicians, and care providers. For example, Hood and Flores also proposed predictive, preventive, personalized and participatory medicine, and termed it as 'P4 Medicine' [5•].

However, systems biology-powered personalized medicine is not without concerns. The Institute of Medicine has published detailed guidelines for translational omics studies [40]. Khoury *et al.* expressed serious concerns on 'P4 medicine' and proposed to add 'a fifth P', that is, the population perspective to the system [41••]. The authors proposed that systems biology should be combined with the ecologic model, and its clinical practice should be contingent on validation with population screening and strong evidence. Moreover, the authors argued that unnecessary disease screening and subclassification might waste limited health care resources instead of reducing the cost and benefiting the patients. Therefore, scientists and physicians developing system biology-powered personalized medicine should practice it with caution. Nonetheless, it is worth noting that accurate sharing of population-based data along with proper interpretation has enormous potential in health care. Individualized information can be compared to similar information from a larger cohort to decide the most effective treatment with the minimal risks of unwanted side effects.

One other foreseeable obstacle for personalized medicine is who develops and provides personalized treatments if the required intervention is beyond available population-based options. Development and test of personalized drugs may lead to formidable costs compared with drugs that target a population. One plausible solution is to develop clinically validated, target-specific compounds for each molecular target in the human body using consortium efforts such as the NCI's Cancer Target Discovery and Development Network [42], and apply personalized treatment with the proper combination of these compounds.

In addition, systems biology-powered personalized medicine depends heavily on technology development and perfection. Presently, none of the current WGS/WES platforms can accurately determine every base of the genome even after effective efforts to boost signal-to-noise ratio [43••,44], and thus the platform-specific variants are usually not rigorously examined [45••,46••]. Therefore any disease causal variants would be missed if they happened to fall in these regions. Biologists need to work closely with computer scientists and hardware engineers to assure continued improvement of current technologies, which will not only improve accuracy and comprehensiveness, but also help bring down the related costs.

Conclusion

Personalized medicine is the future direction of health care and systems biology serves as the enabling force. Despite various clinical and technological concerns, we still believe that personalized health monitoring and preventative medicine will greatly improve the health of the general public. We are envisioning that in the near future, whole genome information will be part of a patient's conventional medical record, and his/her health will be routinely monitored by examining omics profiles either at the clinic or at home. Data generated will be stored securely and hospitals will serve both as an information service and diagnosis and treatment center.

Acknowledgements

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