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Research Articles

Systems Patientomics: The virtual *in-silico* patient

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ABSTRACT

The integration of clinical and molecular sciences with advanced engineering sciences is moving the world towards a new generation of life science where physiological and pathological information from the living human body can be quantitatively described *in silico* via biocomputing across multiple scales of time and size and through diverse hierarchies of organization – from molecules to cells and organs to individuals. The development of the Virtual Patient will change conventional medicine, which has been based upon experience and expectation, into "predictive medicine" that will have the capacity to develop solutions based upon prior understanding of the dynamic mechanisms and the quantitative logic of human physiology. Drug discovery, medical and welfare apparatus, and clinical trials *in silico* will improve the development of products with higher efficiency, reliability and safety while reducing cost. They will also impact upon knowledge-intensive industries. Such program aims at playing a key role in this new area, by sharing and generating solutions as well as human resources contributing to establishment of "*in silico* medicine" as a basis of the predictive medicine within an international framework. In the long-term, computational physiological models will be refined, linked and validated until they are capable of providing essential predictions to clinicians when healthcare decisions need to be made. As the amount of data reinforcing the models grows, predictions will become more and more patient-centred, with models migrating from statistical, average models to physiological and mechanistic models informed by the unique characteristics of the patient. Systems Patientomics will propose new ways of combining this rich patient information space in a highly visual, coherent, meaningful way and of generating new clinical information by blending and fusing existing information, ultimately creating a "Patient Avatar" capable of supporting the medical professional by producing new clinical knowledge emerging from the integration of patient- and population-specific information.

Focal points:

- Benchside
  Quite a few experimental biologists, functional and statistical genomics researchers, involved in developing new measurement technology for biology, and even molecular systems biologists, feel that that computational methods are not relevant for their own research goals. For the lion's share of those cases where these research goals are rationalized by their potential value for predictive, preventive and participatory medicine this is a misconception.
- Bedside
  Systems computational approaches should be a routine part of the clinical arsenal for the diagnosis, planning and executing of therapeutic interventions. This must include the incorporation of relevant training in medical school curricula.
- Industry
  Collaborations to be developed across the breadth of the stakeholder groups involved in public health, from public health providers and patient groups, to researchers, scientists, funders and industry.
- Community
  Development of an ethical and legal framework (establish common rules and principles for data acquisition/sharing/integration/reduction to practice, define how to achieve patient consent, to respond to fears of misuse of provided data, define solutions for data protection/open innovation).

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- Governments
  Governments should faciliate European EHRs adoption for highets quality of patient care.
- Regulatory agencies
  A bypass fast track route for mobile medical apps can be adopted by the FDA authority by working in close relation with app developers, physicians and healthcare givers promote high standards.

"*A picture is worth a thousand words*"

Arthur Brisbane 1911

Today's disease diagnoses are partially decision made by patients' medical histories and partially by symptoms (although patients are often bad at communicating what's really going on with their health). A Johns Hopkins study found that as many as 40,500 patients die in an ICU in the U.S. each year due to misdiagnosis, rivaling the number of deaths from breast cancer [1]. Yet another study found that 'system-related factors', e.g. poor processes, teamwork, and communication, were involved in 65% of studied diagnostic error cases. 'Cognitive factors' were involved in 75%, with 'premature closure' (sticking with the initial diagnosis and ignoring reasonable alternatives) as the most common cause. These types of diagnostic errors also add to rising healthcare expenditures, costing 300,000 USD per malpractice claim [2].

To avoid that healthcare should become more about data-driven deduction and less about trial-and-error. That is hard to pull off without technology, because of the increasing amount of data and research available. *Next-generation medicine* will utilize more complex models of physiology, and more sensor data than a human MD could comprehend, to suggest personalized diagnosis. Thousands of baseline and multi-omic data points and more integrative history will inform each diagnosis. Ever-improving dialog manager systems will help make data capture and exploration from patients more accurate and comprehensive. Data science will be the key to this. In the end, it will reduce costs, reduce physician workloads, and improve patient care.

1. Electronic health records (EHRs) – a starting point

Providing interoperability between different clinical systems, across national boundaries, and integration of clinical systems and research systems lies at the heart of the European Institute for Health Records (EuroRec) and several EU projects, e.g. TransFoRm (Translational Research and Patient Safety in Europe). Significant advances in international standards and in computational technology made possible support of interoperability [3]. Advances in the understanding of clinical judgment and decision making, and the possible ways of supporting them via ICT can inform the design of more 'intelligent' electronic health record systems.

The single richest source of routine healthcare data lies within the records of Europe's General Practitioners. Primary Care is responsible for first contact, continuing, and generalist care of the entire population from birth to death. Any project that aims to comprehensively support the integration of clinical and research data should begin with Primary Care [4]. In addition, even in countries where General Practitioners do not fulfill a 'gatekeeper' function, controlling access to specialist services, the quality of initial diagnosis at Primary Care level determines much of the future course for an individual patient with a health problem. In order to support patient safety in both clinical and research settings, significant ICT challenges need to be overcome in the areas of interoperability, common standards for data integration, data presentation, recording, scalability, and security.

2. Integrating omics data with patient records to improve clinical outcomes – a big data approach

EHRs are an important part of a much larger puzzle. It is now widely accepted that big data can significantly transform health care delivery and improve outcomes for patients everywhere. The "Policy Forum on the Use of Big Data in Health Care" states: "Big data has the power to transform lives. In health care it can reveal the factors that influence health, help target appropriate care for individuals or populations, enable new discoveries, shape outcomes, and reduce costs" [5].

Additionally, the authors of the report, "Embracing the Complexity Of Genomic Data for Personalized Medicine," point out that "Numerous recent studies have demonstrated the use of genomic data, particularly gene expression signatures, as clinical prognostic factors in cancer and other complex diseases" [6]. Big data, in this context, refers to all of the types and varieties of data that are now available and can be integrated with patient information (both health care related and non-health care related) to provide more targeted and effective care and treatment, also known as personalized medicine. Among the data now available is data that is referred to as omic data. In health care, the more popular types of omic data currently being studied include genomics and eventually proteomics. However, several other omics disciplines need attention and they will soon enter mainstream point-to-care testing, as well as multiomics integration with imaging and biosensor data will enable full scope of the big data picture (Fig. 1).

3. Quantified Selfomics: from wearable sensors to mobile medical applications

"2014 will be the year the 'quantified self' goes mainstream." Those were the words Silicon Valley prodigy Marc Andreessen used in a recent article to describe changes about to happen to American healthcare.

The 'quantified self,' also known as lifelogging [6], is a trend toward gathering all possible data about our daily life, such as the food we eat, quality of the air we inhale, our mood, oxygen levels, as well as our physical and mental performance (Fig. 2).

This movement combines smart devices and the Internet of Things with health monitoring apps to give us a better idea of how to optimize virtually every metric associated with our lifestyle, health, and physical performance.

On September 25, 2013, The FDA issued the Mobile Medical Applications Guidance for Industry [7], which explains the agency's oversight of mobile medical apps as devices. These mobile apps fall into the following categories:

1. Mobile platform such as a smartphone transformed into a device already requiring FDA approval, e.g. iPhone into an electrocardiography (ECG) machine.
2. Apps used as an accessory to a regulated device.
3. Mobile medical apps that perform patient-specific analysis and then provide a diagnosis, or treatment recommendations, such as a dosage plan for radiation therapy.