Personalized Medicine: Concepts, Promises, Successes and Challenges

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Abstracts

(By Author)

The rhetoric of enhancement and the reality of technology: The case of personalized medicine
Roger Blumberg (Brown University, U.S.A.)

With the rise and fall of philosophical discussions of technology's essence over the past half-century, we today commonly discuss new technologies and techniques as unique developments in specialized fields, or as particular products for mass markets. The resistance to thinking that all technologies have important features in common leads to ad hoc methods of analyzing and evaluating new technologies, and a general inability to critically evaluate their promise before they have run their course. In this talk I will argue for a particular "essentialist" view of technology that can help us to understand both the achievements and prospects of computing in well-established professions like medicine and education, and, more specifically, to better frame discussions about the promise of "personalized" medicine today.

The revolution of personalized medicine: Are we going to cure all diseases and at what price?
Aaron Ciechanover (Technion-Israel Institute of Technology, Israel)

With the thirty years added to our life span in the 20th century compared to the life span people enjoyed merely 120 years ago, the question is whether the trend will continue, how long will live and whether we will be able to maintain a good quality of life. Much is dependent on modern medicine – availability of new devices and novel drugs and our ability to replace inactive/degenerated tissues with young functional ones. Many important drugs such as penicillin

and aspirin were discovered by serendipity, but we cannot rely on serendipity for systematic development of therapeutic modalities. Other major drugs like statins - the cholesterol biosynthesis inhibitors - were discovered using more advanced technologies such as screening of large chemical libraries using cultured cells as disease models.

One disadvantage of screening is that the process is random and therefore the mechanism of action of the drug we are seeking is not known at the time of its discovery. Also, success depends on the chance discovery of an active compound when screening a library of a myriad of compounds. Another disadvantage is the model on which the screen is based - cultured cells or inbred animals – which do not faithfully reproduce the disease in humans.

Thus, we have begun to realize that patients with the seemingly "same disease" – breast cancer, for example - respond differently to similar treatments. This difference stems from the fact that: (i) human beings carry different genetic repertoires and respond differently to different pathologic cues; and (ii) the apparent "same disease" can evolve in different patients from completely different mechanisms/mutations and therefore have different mechanistic/molecular bases. Thus, breast or prostate cancers (as well as probably almost the entire repertoire of pathologies) can now be sub-divided into smaller distinct classes according to their molecular origins.

As a result, we are leaving behind the era of "one size fits all" treatment for many diseases, and entering a new era of "personalized (or precision) medicine", where the treatment is tailored according to the patient's molecular/biochemical profile. This era will be characterized initially by the development of technologies for sequencing individual genomes, transcriptomes, proteomes and metabolomes, followed by identification and characterization of new disease-specific molecular markers and drug targets, which will be then followed by the design of novel, mechanism-based drugs for these targets. This era will be also accompanied by complex bioethical problems, where genetic information on large populations will become available, and protection of privacy will become an important issue. Also, in many cases planning the treatment and understanding its implications will require the active participation of the patient and his/her family.

Can we do a better genomic-driven precision medicine in oncology?
Moshe Elkabets (Ben-Gurion University of the Negev, Israel)

The overall strategy of targeted therapies - treating cancer patients with drugs that target specific genes or proteins based on their genomic profiling – has shown unsatisfactory clinical outcomes, as for most cases only transient responses have been detected. The only two extreme success stories of Gleevec and Herceptin in treating chronic myeloid leukemia and breast cancer, respectively, highlight the challenges in genomic-driven precision medicine. The limited and transient efficacy of current treatments can be attributed to five major factors: (1) A tumor is a

heterogenic disease with a complex ecosystem (2) Identification of the key "drivers," oncogenes or tumor suppressors, that regulate tumor cell proliferation is crucial. (3) Therapeutic agent quality is not currently satisfactory, and there is a lack of potent drugs that target key drivers. (4) Tumor cells have the ability to adjust to treatment and to rapidly develop resistance mechanisms. (5) Clinical trials are often poorly designed, primarily with a lack of biomarkers of response. We believe that a better understanding of the cancer cells and their ecosystem, together with predicting resistance mechanisms, can lead to the development of clinical trials that will result in better clinical outcomes.

Virtualized drug development for (truly) personalized drug therapy
Hans Lehrach (Max Planck Institute for Molecular Genetics, Germany)

Every patient is different. In particular, every tumor is different. Even subgroups of tumor cells can react differently to specific therapies due to the heterogeneity of many tumors. Drug therapies therefore typically only help a fraction of patients; many patients do not respond, with some suffering sometimes severe side effects of ineffective treatments.

The ability to identify effects and possible side effects of different drugs on individual patients will, in our view, require highly-detailed molecular analyses of every individual patient and his/her individual disease; data that is integral to generating individualized computer models, which can then be used to test the effects of drugs (or other therapies) on the individual.

This will provide a basis for a truly personalized selection of therapies optimal for the individual patient, first in cancer patients, but increasingly also in other areas of medicine and prevention. It will also open the way to an increasing virtualization of the drug development process, by e.g. virtual clinical trials of drug candidates carried out throughout the development process.

Epigenetic approaches in personalized medicine and precision oncology
Frank Lyko (German Cancer Research Center (DKFZ), Germany)

Altered epigenetic modifications have repeatedly been linked to tumor formation. This has resulted in widely-publicized concepts that propose the epigenetic reprogramming of cancer cells into normal cells. However, tumor-associated epigenetic changes are complex and often patient-specific, thus requiring a combination of multiple, highly-specific epigenetic drugs for faithful reprogramming. Despite intense efforts over the past 15 years, these challenges remain to be met on many levels, which raises important questions about the overall significance of the underlying therapeutic concept. Furthermore, it has recently been shown that human tumors maintain the epigenetic program of their cell-of-origin. These interesting new discoveries provide novel opportunities for tumor sub-classification and patient risk stratification. I will present examples

from our own work and discuss how they illustrate the conceptual transition from "personalized" to "precision" oncology.

Ethical aspects and policy tensions in personalized medicine
Eva Winkler (University of Heidelberg, Germany)

The idea behind personalized medicine is to have all relevant sources of information organized around each individual patient. Therefore, the National Research Council in the US chose the analogy of Google maps as an illustration of how we could think about navigating an individual patient's treatment using all relevant data points and biomarkers – be it for prevention or treatment of disease. One prerequisite for realizing this vision is to systematically collect and integrate data generated from research and health care into one "learning health care system". Hence, many countries have set up initiatives that provide the necessary IT infrastructure for the sharing of medical and research data. Their goal is to make data from routine clinical care accessible for various innovative, data-gathering, non-interventional studies or learning activities in order to generate insights that are valuable beyond the diagnosis and treatment of the individual patient. Preparing and utilizing these data by default would benefit society by advancing science and health care.

However, there are potential trade-offs between the opportunities and challenges that personalized medicine poses with regard to ethics and policy in the following areas:

(1) The tension between data-provision and the protection of a person's privacy, especially if genomic sequencing data are used in the context of learning activities
Patients are willing to support and participate in research, but they are also worried about their data being used for marketing and insurance purposes and they are concerned that sensitive information could be widely used and distributed without their knowledge. Especially with regard to genetic data sharing, there is an inherent risk of re-identification.

(2) The tension between the ethics that govern patient care as opposed to research ethics
With the intended permeability of the two thus-far separated fields of care and research, the roles and related responsibilities of researchers as well as physicians change. Are researchers in genomics, for example, responsible for reporting incidental findings with relevance for health? In general, the handling of incidental findings that originate secondary investigation of datasets or primary investigation in the research context is an important challenge for return policies (return of results to the patient).

(3) The tension between principles of evidence-based medicine and fast translation

If genome-wide sequencing is implemented within learning healthcare systems, a wide array of results are generated whose implications are not yet well understood. Returning uncertain information, or using new applications without robust data on their utility, obviously generates ethical and policy issues that personalized medicine programs need to address.

(4) The tension between the ideal of informed consent and the impossibility of informing prospectively about the use of patient data

Collecting patient data and making them available for research later in time challenges the recognized ethical standard of specific consent. Even if models of a broad consent to certain areas of research are acceptable, the broader question still remains of how to involve, communicate and empower patient participation in the use of their data.

The talk will introduce the areas of debate and discuss first solutions as far as they are developed. It will also identify questions that require further discussion.