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Vision Paper by the Editor-in-Chief

"Knowledge-based (personalized) medicine" instead of "evidence-based (cohort) medicine"

Applying nanoscience and computational science to create an effective, safe, curative and affordable medicine of the future

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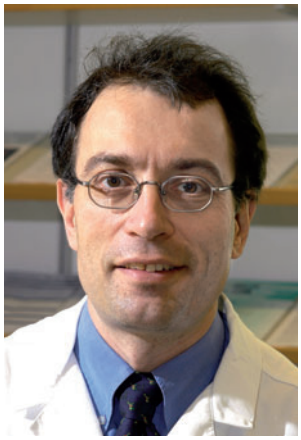

Medicine has moved from phenomenological diagnosis based on syndromes (i.e. a pattern of symptoms and clinical findings) to diagnosis based on imaging and on organ-specific biomarkers, typically assuming a homogenous population. This approach, which often identifies a single disease entity by a single biomarker (like troponin for heart attack, procalcitonin for bacterial infection in respiratory disease, and rapid diagnostic testing for malaria) has been highly successful in identifying frequent diseases and has paved the way to more effective therapy. However, predicting the course of disease in individuals is still a major challenge for clinical reality and experienced physicians refrain from predicting the future in a too assertive manner when consulting their patients. This is due to the fact that a seemingly clear disease entity like myocardial infarction is a continuum in space (location of infarct related artery), time (critical relevance of timing of reopening of occluded artery), severity, and individual factors (degree of subclinical atherosclerosis not related to the event, variability of coagulation system, response to drugs). This inability to predict leads to treatment of individuals who will not benefit from therapy (like platelet inhibition by clopidogrel in clopidogrel nonresponders), while important side effects (e.g., allergic reaction) of drugs can occur even in the absence of patient-specific benefits due to the taking of a particular drug.

Time has come to assess disease not only in a "monomarker" fashion, but to open our eyes to the individuality of each patient and his disease by identifying of the individual biological context (e.g., genetic variabilities in metabolism, immune system state, coagulation system), in its temporal dimension.

1. The quest for nanoscience and computational-science based tools for personalized patient management

Nanoscience based technologies for fast and deep genomic sequencing, for proteomic and metabolomic analysis will play a big role in understanding the many facets of a patient's state.

However, progressing beyond single biomarkers towards a more comprehensive understanding is a major challenge for current medical practice: recent developments towards "evidence-based medicine" and a guideline-driven practice have driven medical practice in the opposite direction: assuming that multicenter megatrials comprising a broad mix of patients would yield the ultimate truth about the value of single drugs for single disease entities, largely neglecting the individuality of a patient. Also, daily practice is strongly influenced by simplistic "standard operating procedures" because those are simple to memorize.

2. The quest for computational science tools for personalized medicine in clinical practice

This implies that a key success factor for personalized medicine in clinical practice are tools that allow to draw valid and predictive conclusions from the complexities of a full genomic and proteomic assessment of a given patient, and that allow to choose not only a personalized drug, but also an optimized drug dose, drug schedule and therapy duration or an optimal drug combination based on suited disease models. An interdisciplinary effort combining clinical medicine, nanotech diagnosis, genomics, and computational science is required to develop such predictive models and to validate them in clinical practice.

3. The quest for more effective, safer, affordable therapies and a perspective of cure instead of disease suppression

The "number needed to treat" (NNT) is an established number to quantify a therapeutic benefit to patients and expresses the number of patients that need to be treated to prevent a single major event in a patient (1). If the NNT equals 1, each patient treated benefits from the therapy. In practice, NNTs between 10 and >100 for common diseases like heart attack or hip fracture are common. Another number quantifying the benefit to the patient is "postponement", i.e. the average increase in time delay to the occurence of a major event in the entire treated population (2). Analysis of these numbers shows that in many therapies a minority of patients draw a major benefit from treatment, but a majority of patient do not actually benefit significantly, while still allowing the number or degree of side effects and the cost of drugs to increase. The limitation on today's medicine is very visible in the field of oncology, where cancer chemotherapy is often able to postpone death by cancer, but rarely able to cure it. Thus, it is evident that a major driver of cost in healthcare is our inability to predict who will benefit as well as our inability to cure them.

Nanomedicine is on the way to profoundly change the efficacy/safety profile of many drugs through targeted delivery based on molecular understanding in a personalized fashion. This is currently best visible in novel cancer therapies: by achieving high drug doses in diseased tissues while limiting drug concentration in remote, healthy tissues, it is possible to achieve cancer cures in mice at a significantly higher success rate compared to conventional therapies, in particular if molecular targeting strategies are applied. Hopefully, we will see translation of these results (already visible in a limited number of clinical trials) to broad clinical practice soon. While oncology is a pioneering field with respect to application of nanomedical therapies, there is a need to progress towards a curative approach also for other diseases of comparable severity (namely inflammation/infection, cardiovascular disease, and brain diseases), of high prevalence, or of similar economic burden.

Today's medicine is reasonably effective but also quite expensive, thereby limiting access to healthcare for important segments of the world population. While new developments in medicine always carry a price tag, the high "numbers needed to treat" in current medical practice show that there is also ample opportunity to save expenses by focusing therapies on those who will really profit from them, made possible on the basis of a deeper knowledge and more detailed understanding of disease in individuals through nanoscience-enabled diagnostic tools.

Moving from the currently dominant palliative treatment schemes to persistent cure will also free up significant resources from their currently ineffective use for more effective therapies. A transition from palliative to curative therapies in the fields of cancer, cardiovascular disease, diabetes and dementia will thus not only allow us to spend more of our lifetime in good health but also enable a reduction of indirect health-related costs, which already now exceed direct healthcare spending.

Nanomedicine is the horizon, and it promises not only better and safer "standard" therapies but also a curative approach to important diseases and a highly cost-efficient medical practice by spearheading a *personalized, knowledge-based medicine.*

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