Personalized medicine: a perspective on the patient, disease and causal diagnostics

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In this commentary, I intend to use my 'invitation to be provocative' to provide my thoughts on the difference between the concept and the practice of several themes that have become both investment and strategy buzzwords, such as translational research, systems biology and personalized medicine, and the gap between where they are today and their ability to truly address patient and physician needs. My goal is to provoke thought and discussion about bridging the gaps between research and clinical utility for improving patient care and quality of life (QoL). This, to me, means understanding the differences between the disease, the patient and how they separately develop and interact.

A simple Google™ search indicates incredible activity in each of these areas, with over 1,000,000 hits for 'personalized medicine' (compared with >52,000,000 for 'medicine'), over 250,000 for 'translational medicine or research' and over 900,000 for 'systems biology'. This probably reflects the diversity in interpretation and application of these terms rather than deep, focused efforts along specific research tracks. More importantly, I believe that these concepts have generally evolved from a focus on technology rather than a focus on clinical need, although their stated goals are to improve patient care. A fundamental problem that exists within the scientific community is the perception that 'more data' implies 'more knowledge'. This reflects an incomplete appreciation of the significant chasm between data and knowledge and the even greater gap that exists when we evaluate knowledge in terms of clinical utility.

For the purposes of this article, I provide my definitions of these terms and recognize that they may not be universal in their acceptance or use. While it is critical to understand these concepts individually, it is their synergies that will provide the basis for improving patient care and QoL.

Translational research

Translational research targets the conversion of laboratory results into clinical utility; however, translational research must start in the clinic and not at the laboratory bench, with the identification and communication of clinically significant problems into the laboratory for research and resolution. The only true measure of success of this targeted research is in terms of what translates into the clinic. Unfortunately, this is currently somewhat limited because the driving force still appears to be academically focused research rather than clinically established needs [1–3,101,102].

Systems biology

Systems biology is commonly interpreted as the aggregation and integration of multiple approaches to analyze and define a system, such as the 'omics' perspective, and then perform analysis of the behavior of the system through these perspectives. This 'bottom-up' approach can only bring together the views available through the application of existing and evolving technologies. It is easy to see that a limitation of this approach is the expectation that these technologies provide a complete picture of the entity rather than a more focused deconvolution of the problem at hand. Of course, these technologies are neither comprehensive enough to provide a complete picture of a patient, nor are they necessarily of equivalent quality or content. I recommend moving towards a 'top-down' approach to systems biology, examining the behavior of the system, such as a patient with or without disease symptoms, to identify the question in need of resolution and the technology appropriate for resolving these issues. However, all results must be integrated into a comprehensive, patient-centric data model [4,103]. It should be clear that this top-down approach aligns directly with the translational medicine definition above.

Personalized medicine

Personalized medicine has focused on optimizing treatment to maximize efficacy and minimize risk, in this case therapeutic medicine, using the genetic make-up of the patient. However [101]:

> *"Medicine is … concerned with maintaining or restoring human health through the study, diagnosis, treatment and possible prevention of disease and injury."*

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Ideally, personalized medicine should incorporate and promote a significant component of preventive medicine, thus aligning more closely with the non-US clinical perspective where prevention is a major focus of healthcare that is frequently based on a single-payer system. More importantly, restricting the approach to include only genetic information may significantly limit impact, both in its application to clinical practice and its ability to support broader research goals. However, within the frameworks of translational research and systems biology, as stated above, personalized medicine can evolve to achieve its broadest goal, the improvement of patient care [5].

Confronted with an emphasis on treatment rather than prevention, these activities have focused on the development of diagnostics and/or therapeutics to directly affect treatment, rather than understanding the fundamental aspects of the underlying disease or the physiological and psychological state of the patient. It is readily observed that breast cancer appears and behaves differently in pre- compared with postmenopausal women. Is this the same disease in a developmentally different host or does it reflect different diseases beyond estrogen and progesterone status? Statistical evidence also relates risk for breast cancer with smoking, alcohol-use and body-weight factors. These risks are not uniform throughout a patient's lifetime. For example, the breast undergoes developmental changes continuously during the *in utero* to postmenopausal transition and the mechanistic basis for this risk is probably related, in part, to differences in gene and protein expression and protein modification that will accompany these developmental changes. The complexity of the underlying biological relationship between patient and disease has not been adequately addressed by translational research/systems biology/personalized medicine to date; it requires refocusing their potential to describe these underlying processes. A fundamental aspect of this complexity is the fact that disease, although frequently described in terms of 'disease state', actually represents a process that evolves over time through an integrative relationship involving the patient's genetics and their interaction with lifestyle and environmental factors, which always starts significantly before any symptoms may appear. The key to tackling this complex relationship comes from the integration of the approaches defined above; however, the essential requirement is to define separately the characteristics of the patient from those of the disease.

A patient possesses intrinsic characteristics (those derived from their genetic make-up and its expression in their underlying physiological structures) and extrinsic factors (such as their lifestyle and environmental exposures, including physical activity, smoking behaviors and alcohol consumption). The disease represents a pattern of actions that interact with, and are modified by, these characteristics. The conundrum is how to identify and separate the extensible definitions of disease from those that are dependent on the patient in terms of intrinsic and extrinsic characteristics. Thus, the presentation of disease exceeds the simple sum of its parts, namely, the patient and the disease process. For biomarkers/diagnostics to be effective in specifying targets and/or levels for appropriate intervention, it becomes critical to interpret and resolve the complexity of the disease–patient interaction.

To better define the patient, we have been developing a personalized health record that spans the life history of the patient and treats the data in a chronological record, including, but not limited to, family history (at a genetic analysis level), history of diagnoses/illnesses, treatments and response, and lifetime exposure to environmental and lifestyle risk factors, such as smoking, body mass index or alcohol consumption [6]. In collaboration with InforSense Ltd, we have developed a patient-modeling environment to support fuzzy querying about patient-based characteristics in qualitative and quantitative time relationships for the purpose of identifying critical co-occurrence information about diseases and risks. This enables a physician to represent the detailed history of a specific patient and, also, compare/search the database for, for example, other patients with similar patterns of disease for use in evaluating treatment options. With Concentia Digital, Inc., this capability has been extended to include diagnostic and research images. The examination of co-occurrence of disease [7] or systemic problems is thus examined from both an epidemiologic and mechanistic perspective, involving collaboration with BIOBASE and its pathway databases and the use of stochastic activity modeling approaches to support the evaluation of genotypic variation and/or drug interactions in the patient.

Enhancing the accuracy in defining disease remains extremely elusive because of the tendency to group potential disease subtypes under simple classifications, such as breast cancer. Among the elements critical to more accurately defining a disease subtype is the need to identify quantifiable characteristics, including disease progression or (sub)pathologies, that can readily complement the current trend towards stratification using gene-expression technology alone. Using the concepts of disease progression and disease process as noted above, it should be invaluable to measure and analyze the clinical parameters longitudinally and not just at the time of diagnosis. It should be noted that most diagnostics/biomarkers have been developed because of their correlative relationship with a disease diagnosis or state and not because of a quantifiable recognition of their mechanistic relationship with disease symptoms. We have defined disease stratification as the longitudinal path or vector through clinical parameters that can be observed for a patient, which may occur in multiple dimensions, each one reflecting a clinical observation. Thus, where we are measuring more than 600 clinical parameters and additional molecular descriptors, longitudinally, a patient can be algorithmically represented as moving through a 600-dimensional space. Disease stratification involves identifying the significant clusters of this longitudinal progression and the concomitant reduction of dimensionality necessary to describe the disease pathway. Thus, disease staging is the observation of how far along a disease path a patient has progressed [8]. Clinical ambiguities may exist when two patients exhibit similar diagnostic values but on different disease paths. This can be due to the correlative relationship of the biomarker and the fact that these patients may be at different time-points along their separate disease paths, which overlap in one or more dimensions (clinical parameters). Conversely, two patients may appear ‘diagnostically’ different when they are on the same disease path but have been observed at different disease stages. This dilemma is faced by physicians daily and its resolution relies on the experience and knowledge of the practitioner. To truly develop diagnostics, biomarkers and the area of personalized medicine, it will be critical to analyze and interpret the longitudinal nature of disease in a more quantifiable manner to reflect its true complexity.

This process of stratification of patient compared with stratification of disease will not be one that is readily solvable with current patterns of patient information, record keeping or sole dependency on, for example, genomic information. Rather, it will require extensive, recursive modeling of the complexity of the relationship that truly defines the patient–disease relationship.

There must also be an evaluation, based on issues of QoL for the patient and their family, access to technology and cost–benefit analysis of its application, to determine which diseases and/or patients this analysis will become critical for. These issues will quickly move beyond the question of access to technology to touch upon the cultural and ethical boundaries and sensitivities that currently exist. However, in order to become truly effective, the reality of personalized medicine and the development of effective diagnostics that support improvement of QoL for the patient must anticipate and deliver on the integration of all these factors.

Executive summary

- Translational research, systems biology and personalized medicine have approached the complex situation of healthcare from a technology-based, bottom-up approach. The significant opportunity to couple this with a top-down approach, using clinical data to stratify the complexity of the disease before stratifying the molecular characteristics of the patient, should provide new insight into the deconvolution of the disease process from the patient with the disease. Overall, the ultimate goal is to improve patient care and quality of life issues for the patient, and this requires a close link to the clinician and clinical perspective as the driving force for, for example, genomic, genetic and proteomic research.
- There is a significant gap between data, information, knowledge and utility.
- Disease is a not a discrete state; rather, it is a process that evolves over time.
- Disease stratification needs to incorporate longitudinal data and high-dimensional clustering.
- Disease staging is the evaluation of how far along a disease pathway a patient has progressed.
- Intrinsic patient parameters include genetic makeup; extrinsic parameters include lifestyle and environmental factors.
- Comprehensive diagnosis requires the separate evaluation of the patient’s physiological and developmental status and the subtype of disease that is present.
- Translational research, systems biology and personalized medicine are approaches whose technological focus can be brought to bear synergistically to improve patient care and quality of life.

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